Medical Countermeasure Models Volume 4: *Francisella tularensis*

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14. ABSTRACT

The F. tularensis medical countermeasure model presented here allows users to explore how medical countermeasures (MCM) can impact the course of the disease, mortality, and loss of work. The model is designed to allow users to input information about exposure and countermeasures, run a simulation and display outputs. The parameters describing disease outcomes for patients with no MCM that underlie the model are informed by parameters established by Curling et al, while the parameters describing the efficacy of MCM were established specifically for this project using publicly available data from human and animal studies. This stochastic model allows users to input data about each exposed individual including the number of bacteria inhaled, vaccination status, timing and duration of antibiotic post-exposure prophylaxis, and treatment status and timing. After the model is run, the output tab displays the outcome for each individual. The graph tab provides a summary of the results, including the percent of individuals that die, recover, or never develop illness, as well as the time distributions of symptom onset and death. The sample results included in this report demonstrate how MCM can impact the number of casualties, the timing of the disease, and the number of days of work lost. Users of the model can explore additional scenarios by modifying the dose and MCM inputs.

15. SUBJECT TERMS
F. tularensis; tularemia; MCM; countermeasure; LVS; antibiotics; PEP; work lost; casualties; model

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Preface

The research and development work described in this report was conducted under the Joint Science and Technology Office (JSTO) of the Department of Defense (DoD) Chemical and Biological Defense (CBD) Program. JSTO is also the Chemical/Biological Technologies (CB) Directorate in the Research and Development (RD) Enterprise of the Defense Threat Reduction Agency (DTRA). Contract HDTRA1-10-C-0025 is titled *Medical Countermeasures for CBR Agents*.

This project was initiated by Ms. Nancy Nurthen of the Information Systems Capability Development Division (RD-CBI), and was transitioned to Dr. Christopher Kiley at RD-CBI for the first option year. It was funded under DTRA Contract Number HDTRA1-10-C-0025 to Gryphon Scientific, LLC, with subcontractor Applied Research Associates, Inc. (ARA). The target application for the product of this contract is To Be Determined (TBD) under the auspices of the Joint Project Manager for Information Systems (JPM IS) of the Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD).

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Executive Summary

The *F. tularensis* medical countermeasure model presented here allows users to explore how medical countermeasures (MCM) can impact the course of the disease, mortality, and loss of work. The model is designed to allow users to input information about exposure and countermeasures, run a simulation and display outputs. The parameters describing disease outcomes for patients with no MCM that underlie the model are informed by parameters established by Curling et al, while the parameters describing the efficacy of MCM were established specifically for this project using publicly available data from human and animal studies. This stochastic model allows users to input data about each exposed individual including the number of bacteria inhaled, vaccination status, timing and duration of antibiotic post-exposure prophylaxis, and treatment status and timing. After the model is run, the output tab displays the outcome for each individual. The graph tab provides a summary of the results, including the percent of individuals that die, recover, or never develop illness, as well as the time distributions of symptom onset and death. The sample results included in this report demonstrate how MCM can impact the number of casualties, the timing of the disease, and the number of days of work lost. Users of the model can explore additional scenarios by modifying the dose and MCM inputs.

Introduction

Accurate modeling of medical countermeasure efficacy against chemical, biological and radiological (CBR) agents is essential to understanding the vulnerabilities of our warfighters on the modern battlefield. In helping calculate the benefit of countermeasures, modeling can inform data-driven purchasing decisions and logistical tradeoffs. In this study, Gryphon Scientific and Applied Research Associates (ARA) developed models to predict the efficacy of medical countermeasures against a variety of agents.

This report (prepared by Gryphon Scientific) is one of ten describing the medical countermeasure models constructed for this project. This volume focuses exclusively on the methods used to construct the *F. tularensis* model, instructs the user on how to use the model, and provides examples of the outputs generated by the model. Other volumes describe models for *B. anthracis* (volume 1), organophosphates (volume 2), cesium-137 (volume 3), sulfur mustard (volume 5), americium-241 (volume 6), *Y. pestis* (volume 7), botulinum neurotoxin (volume 8), plutonium-238/239 (volume 9), and vesicants (volume 10, an expansion on volume 5). Each volume begins by briefly introducing the agent modeled and the countermeasures available for use against the agent. The overall schematic of each model and the relevant parameters are then discussed, along with a brief explanation of the rationale for selecting each parameter. Lastly, this report discusses the calculations and computational framework of the Microsoft Excel Model and provides examples of modeling outputs.

Summary of Deliverables

Below is a description of the four deliverables assigned for each agent of interest, and a description of what is included in each deliverable. The item in bold (number four, the "MCM Model Built in Microsoft Excel") is the deliverable presented in this final report.

1. Modeling Approach

   The modeling approach deliverable describes each of the parameters that we anticipate including in our MCM model. For each parameter, a description of the approach for developing and justifying the parameter is presented. The approach developed is based on prior knowledge of the agent and on the general types of data available for each agent, but specific citations are not included as it is a preliminary document.

2. Modeling Parameters

   The modeling parameters deliverable defines the value or function for each parameter used to develop the MCM model. Each parameter is supported with a description of the rationale for choosing the parameter, including any scientific evidence used in parameter development or assumptions that were made.

3. MCM Model

   In addition to the information already developed in the "Modeling Parameters" deliverable, the "MCM Model" includes a description of the model, user inputs, the model calculations, and the model outputs. For the biological agents, the report is an accompaniment to a preliminary implementation of the MCM model built in Microsoft Excel.

4. MCM Model Built in Microsoft Excel

Microsoft Excel is used for the final implementation of the biological MCM models. This implementation of the model includes feedback and adjustments made after review of the previous deliverables, and will be available for independent verification and validation.

Francisella tularensis

Overview

Francisella tularensis, the etiologic agent of tularemia, is a zoonosis existing primarily in rodent and small mammal populations and is only occasionally transferred to humans. The bacterium is an aerobic, gram-negative coccobacillus with a thin lipopolysaccharide envelope, and is an intracellular organism that multiplies primarily within macrophages. Although the exact route of pathogenesis is not entirely clear, it is known that the bacteria can travel to the lymph nodes, spleen and liver before infiltrating the blood and other tissues.[1] The disease, which individuals can sometimes recover from even in the absence of treatment, can overwhelm the infected organs, causing necrosis and eventually death. Though it does not form spores, *F. tularensis* is still very hardy and capable of surviving at low temperatures for weeks. This characteristic makes weaponization possible, a fact that has led to its study as a warfare agent by both the US and foreign governments.[2]

There are two clinically relevant types (or biovars) of *F. tularensis*. Type A (*F. tularensis* subsp *tualarensis*) is the most virulent in humans, and is found exclusively in North America. Type B (*F. tularensis* subsp *holartica*) is found across North America, Europe, and Asia and is significantly less virulent in humans. The other two subspecies (subsp *mediasiatica* and subsp *novicida*) are less pathogenic and rarely cause disease in immunocompetent individuals. Due to its high pathogenicity in humans, Type A *F. tularensis* is the subspecies most likely to be used in a bioweapon and, therefore, is the focus of our analysis (see "Determining Human Clinical Case Biovars" in Appendix 5 for more information).[3]

Although *F. tularensis* can cause disease via a vector (by penetrating the skin) or via ingestion (by penetrating the mucous membrane of the gastrointestinal tract), our model assumes exposure via inhalation, since this is the most likely route of infection on a battlefield. Inhalational exposure causes acute febrile illness with pneumonic symptoms. Pneumonia is not always present after inhalation; in some cases systemic disease can manifest without pulmonary involvement. Other infection types are also possible after aerosol exposure, including pharyngitis, conjunctivitis, or cutaneous infection via broken skin.[4] Our model assumes that the cases of tularemia would result from inhalation of the bacteria, since only a very limited number of illnesses would be caused by infection at these alternate sites.

Countermeasures

Countermeasures against *F. tularensis* include vaccines and antibiotics, both of which have efficacy at one or more stages of the disease. When administered prior to exposure, the tularemia vaccine, LVS (Live Vaccine Strain), can prevent the onset of disease in some individuals and decrease the severity of disease in others. Though LVS was awarded investigational new drug status in the early 1960s, it is currently unavailable.[5,6] Antibiotics can be administered either as post-exposure prophylaxis (PEP) before the onset of symptoms or as treatment after the onset of symptoms.

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1 Chen W et al. "Toll-like receptor 4 (TLR4) does not confer a resistance advantage on mice against low-dose aerosol infection with virulent type A *Francisella tularensis*." *Microbial Pathogenesis*. **37**(4). 2004.

2 Dennis DT et al. "Consensus Statement: Tularemia as a Biological Weapon: Medical and Public Health Management." *JAMA.* **285(**21). 2001.

3 Champion MD et al. "Comparative genomic characterization of *Francisella tularensis* strains belonging to low and high virulence subspecies." *PLoS Pathology*. **5**(5). 2009.

4 Dennis DT et al. "Consensus Statement: Tularemia as a Biological Weapon: Medical and Public Health Management." *JAMA.* **285(**21). 2001.

5 Conlan J and Oyston P. "Vaccines against *Francisella tularensis*." *Annals of the New York Academy of Sciences*. **1105**. 2007.

Model Overview

We have developed a stochastic model of the efficacy of medical countermeasures (MCM) against *F. tularensis*. Given a description of agent exposure, prophylaxis and treatment, the model calculates the likely outcome in terms of morbidity, mortality and loss of work due to both the agent itself, and any adverse medical countermeasure side effects. The evidence-based parameters, which form the basis of the model, determine the probability of each outcome; the model then draws a random number to determine which outcome is realized for any individual by comparing it to the probability of the outcome.

A schematic of the tularemia MCM model illustrates where each piece of data is applied and how the model functions (Figure 1). Inputs are indicated by light blue ovals and include dose of agent, pre-exposure vaccine status, availability of antibiotic post-exposure prophylaxis (PEP), and availability of treatment. Each of the inputs feeds into the modeling calculations indicated by dark blue rectangles. Purple rectangles represent intermediate outcomes, while terminal model outputs are represented by red rectangles and include death, survival with no loss of work, or survival with loss of work.

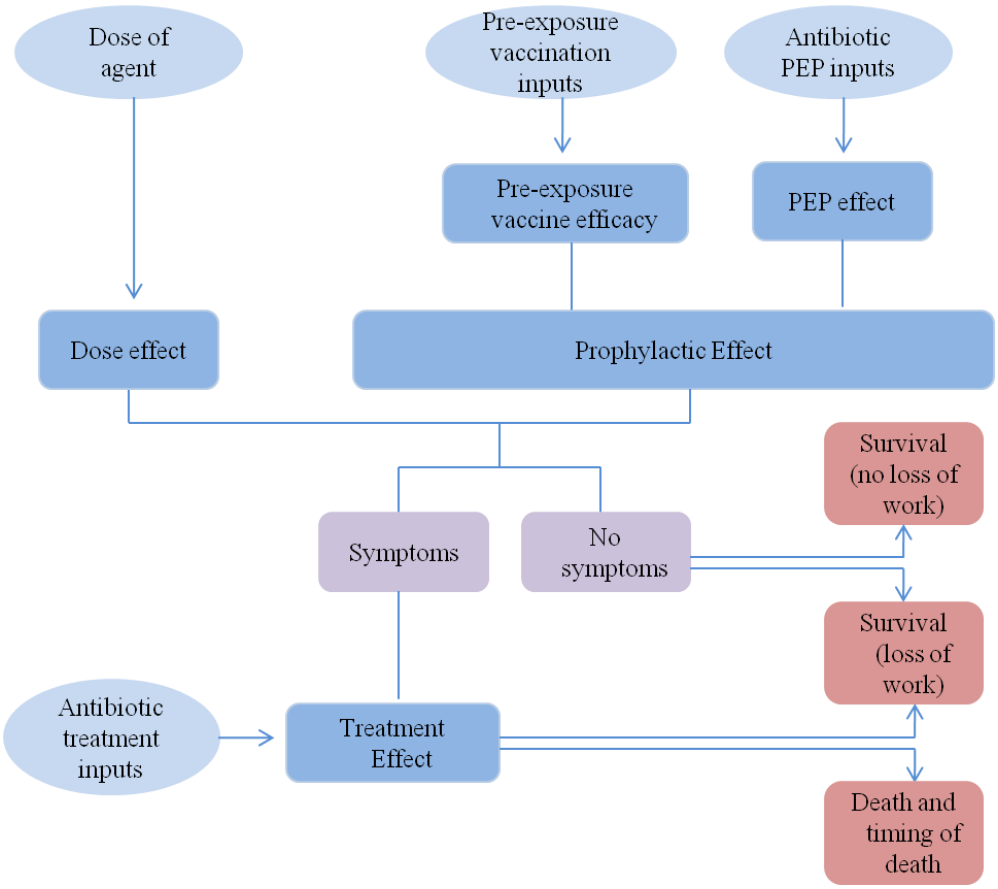
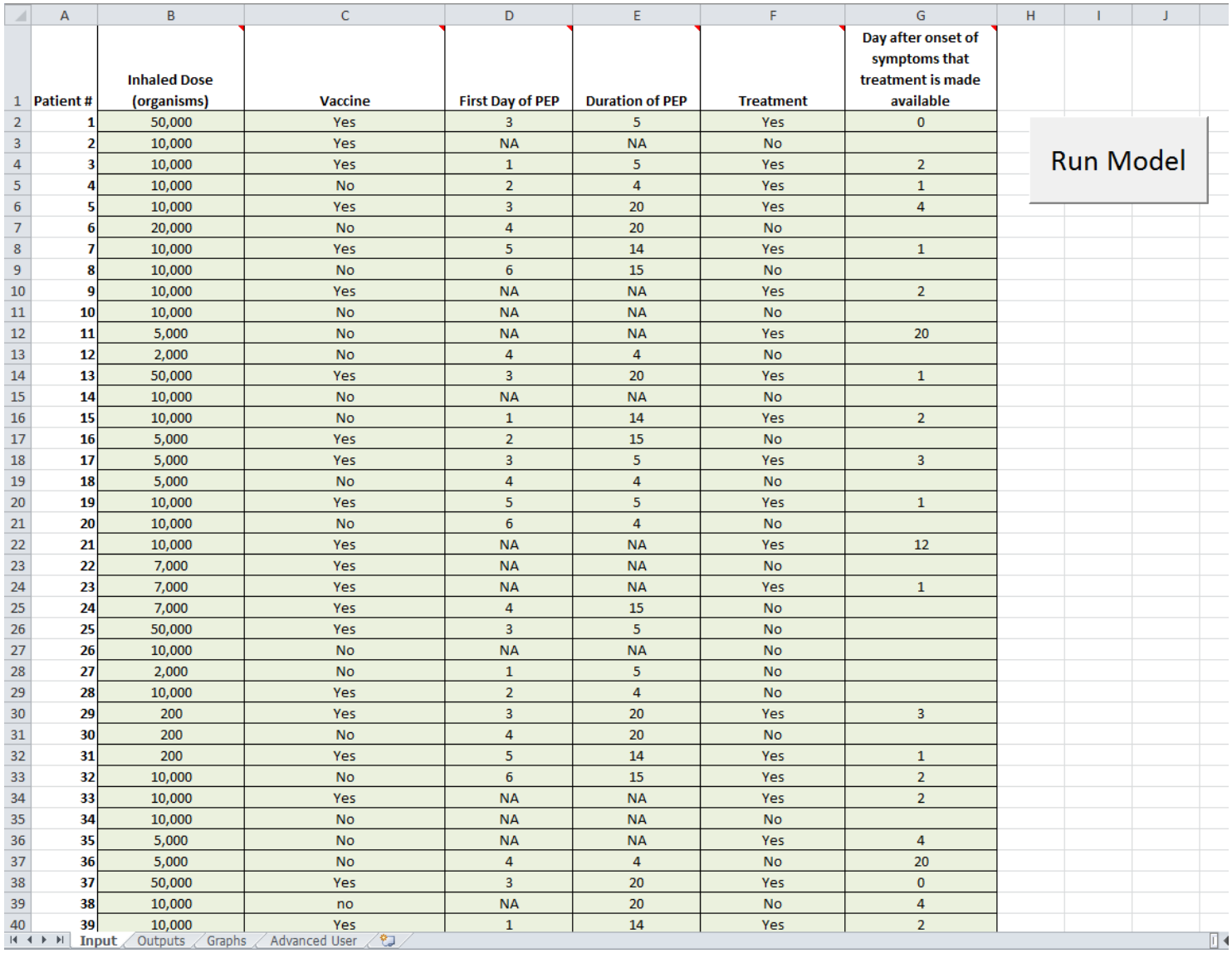


Figure 1. Tularemia modeling scheme. Blue ovals indicate user inputs, blue rectangles indicate modeling parameter calculations, purple rectangles represent intermediate outcomes and red rectangles are terminal model outputs.

[6] Pechous R et al. "Working toward the future: insights into *Francisella tularensis* pathogenesis and vaccine development." *Microbiology and Molecular Biology Reviews*, **73**(4). 2009.

Microsoft Excel Model Overview

The model operates in Microsoft Excel and has four tabs available to the users: "Inputs," "Outputs," "Graphs," and "Advanced User". The modeling calculations are on tabs hidden from the user. On the "Inputs" tab, exposure and MCM conditions can be entered separately for each individual (Figure 2). To understand outcomes for a group of individuals, the user should use the "copy and paste" tool to input multiple individuals with the same characteristics. For example, given data from 10,000 cases in which 50% were treated with antibiotics, 5,000 would be entered as identical treated individuals and 5,000 would be entered as identical untreated individuals.



Patient #	Inhaled Dose (organisms)	Vaccine	First Day of PEP	Duration of PEP	Treatment	Day after onset of symptoms that treatment is made available
1	50,000	Yes	3	5	Yes	0
2	10,000	Yes	NA	NA	No	
3	10,000	Yes	1	5	Yes	2
4	10,000	No	2	4	Yes	1
5	10,000	Yes	3	20	Yes	4
6	20,000	No	4	20	No	
7	10,000	Yes	5	14	Yes	1
8	10,000	No	6	15	No	
9	10,000	Yes	NA	NA	Yes	2
10	10,000	No	NA	NA	No	
11	5,000	No	NA	NA	Yes	20
12	2,000	No	4	4	No	
13	50,000	Yes	3	20	Yes	1
14	10,000	No	NA	NA	No	
15	10,000	No	1	14	Yes	2
16	5,000	Yes	2	15	No	
17	5,000	Yes	3	5	Yes	3
18	5,000	No	4	4	No	
19	10,000	Yes	5	5	Yes	1
20	10,000	No	6	4	No	
21	10,000	Yes	NA	NA	Yes	12
22	7,000	Yes	NA	NA	No	
23	7,000	Yes	NA	NA	Yes	1
24	7,000	Yes	4	15	No	
25	50,000	Yes	3	5	No	
26	10,000	No	NA	NA	No	
27	2,000	No	1	5	No	
28	10,000	Yes	2	4	No	
29	200	Yes	3	20	Yes	3
30	200	No	4	20	No	
31	200	Yes	5	14	Yes	1
32	10,000	No	6	15	Yes	2
33	10,000	Yes	NA	NA	Yes	2
34	10,000	No	NA	NA	No	
35	5,000	No	NA	NA	Yes	4
36	5,000	No	4	4	No	20
37	50,000	Yes	3	20	Yes	0
38	10,000	no	NA	20	No	4
39	10,000	Yes	1	14	Yes	2

Figure 2. Screen shot of "Inputs" tab

Table 1, below, gives detailed information about each of the user input options shown in Figure 2 and explains how each input should be used.

Table 1. MCM Model Inputs	
Input Category	**Explanation of Input**
Dose of Agent	
Inhaled dose	Designates the number of inhaled organisms.
Vaccination Inputs	
Vaccine	Designates whether or not an individual receives a vaccine prior to exposure using Yes/No options.
Antibiotic PEP Inputs	
First day of PEP	Designates what day post-exposure prophylactic antibiotics are first made available. If the first day that PEP is available is on or after the first day of symptoms, the PEP inputs are ignored. The user must enter "NA" for any individuals that will not have PEP made available. For all others, the user must select the day the PEP is first available. Zero indicates that PEP is first available on the day of exposure. If this input is left blank, the model assumes that prophylactic post-exposure antibiotics are made available on the day of exposure.
Duration of PEP	Designates how many days an individual remains on PEP, assuming that PEP is available before the onset of symptoms. If PEP is not made available before the onset of symptoms this input is ignored. The model also ignores this value if "NA" is selected for "First day of PEP." If a value is selected for "First day of PEP" and the "Duration of PEP" input box is left blank or filled with a zero, the model assumes PEP is discontinued on the same day it is started. "NA" should not be entered in the "Duration of PEP" field if a value is selected for "First day of PEP" as this will result in an error.
Treatment Inputs	
Treatment	Using Yes/No options, designates if antibiotics are available for treatment (if needed). If a treatment is selected, but the model determines the individual will not develop symptoms, the treatment is not used.
Day after onset of symptoms that treatment is made available	Designates how many days after the onset of symptoms that treatment is made available. Zero indicates that treatment is made available on the day of symptom onset, and an input of one indicates that treatment is available the day after symptom onset. If a value is input here, but no treatment is selected, the number will be ignored. If a treatment is selected and the "First day of treatment after onset of symptoms" input box is left blank, the model will assume that treatment is started on day zero, the day symptoms first appear.

Once all the user-defined parameters are entered, the "Run Model" button will start the calculations. When the model has finished running, the "Graphs" tab is automatically selected (Figure 3). In this tab, the results are described in a summary box that includes the total number of individuals exposed to *F. tularensis*, the number that develop symptoms, the number that die, the total number of individuals that lose work and the total number of days of work lost due to medical countermeasures and illness, and the total number of individuals with chronic tularemia. This tab also includes a pie chart of the outcomes (percent dead, recovered, and not sick), and scatter plots of the time distributions of symptom onset and death.

Users who wish to view a more detailed account of each individual's outcome can select the "Outputs" tab. Here, the user can again view the summary box seen on the "Graphs" tab. Results for each individual are also presented as applicable, including outcome, time of symptom onset, period of fever, day of death, days of work lost due to MCM adverse effects, days of work lost due to illness, day of relapse, and whether or not chronic tularemia develops in the patient (Figure 4).

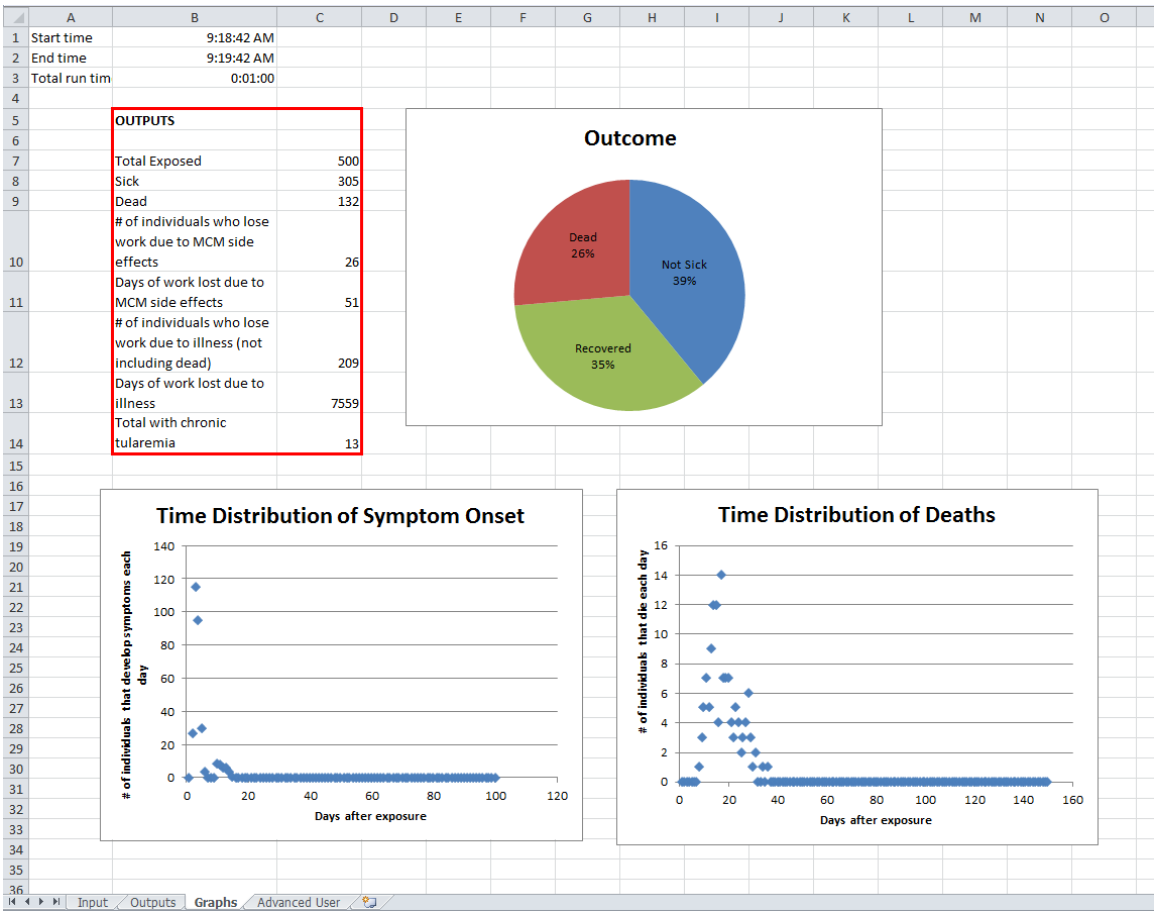
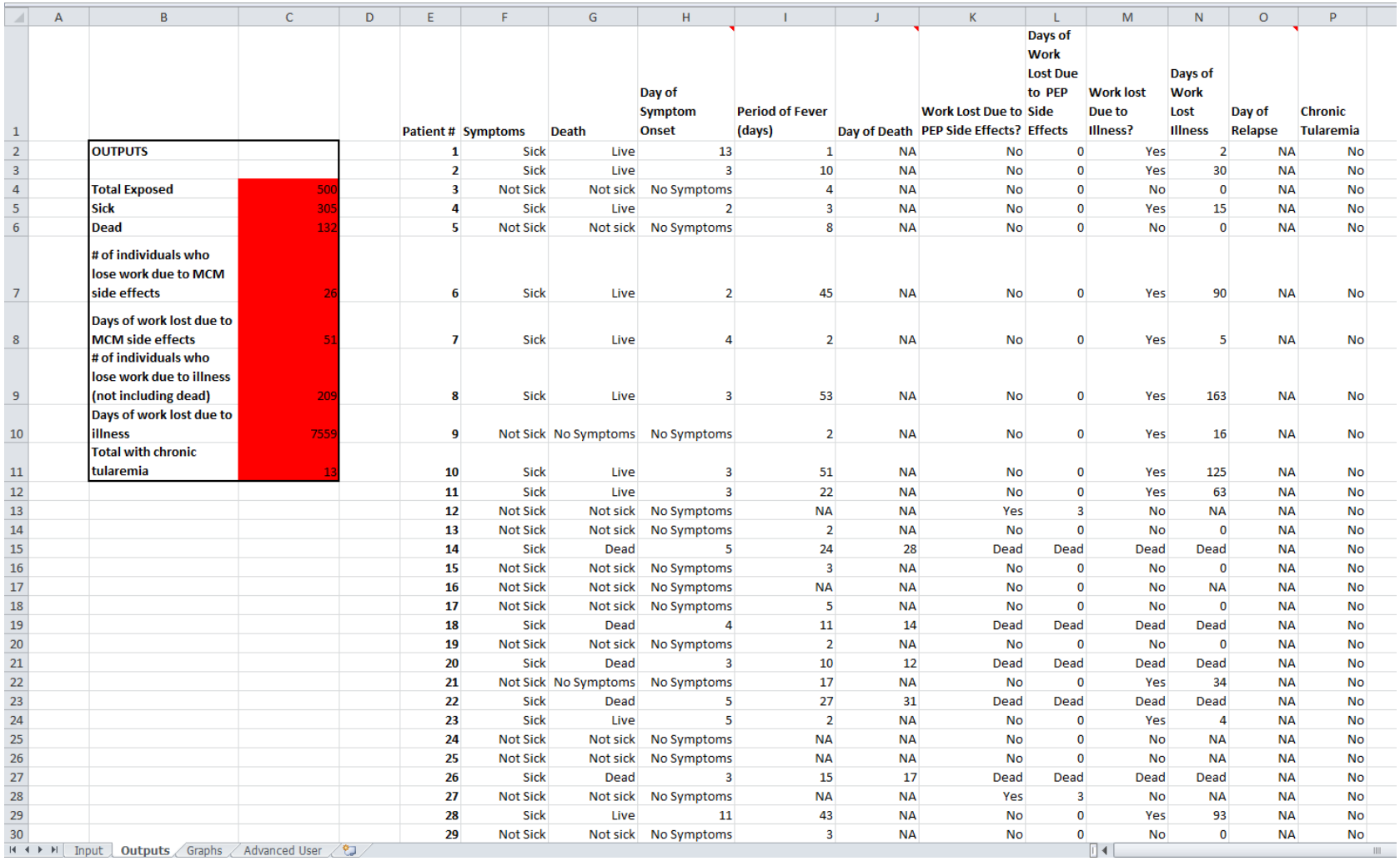


Figure 3. Screen shot of "Graphs" tab



	B	C	Patient #	Symptoms	Death	Day of Symptom Onset	Period of Fever (days)	Day of Death	Work Lost Due to PEP Side Effects?	Days of Work Lost Due to PEP Side Effects	Work lost Due to Illness?	Days of Work Lost Illness	Day of Relapse	Chronic Tularemia
1														
2	OUTPUTS		1	Sick	Live	13	1	NA	No	0	Yes	2	NA	No
3			2	Sick	Live	3	10	NA	No	0	Yes	30	NA	No
4	Total Exposed	500	3	Not Sick	Not sick	No Symptoms	4	NA	No	0	No	0	NA	No
5	Sick	305	4	Sick	Live	2	3	NA	No	0	Yes	15	NA	No
6	Dead	132	5	Not Sick	Not sick	No Symptoms	8	NA	No	0	No	0	NA	No
7	# of individuals who lose work due to MCM side effects	26	6	Sick	Live	2	45	NA	No	0	Yes	90	NA	No
8	Days of work lost due to MCM side effects	51	7	Sick	Live	4	2	NA	No	0	Yes	5	NA	No
9	# of individuals who lose work due to illness (not including dead)	209	8	Sick	Live	3	53	NA	No	0	Yes	163	NA	No
10	Days of work lost due to illness	7559	9	Not Sick	No Symptoms	No Symptoms	2	NA	No	0	Yes	16	NA	No
11	Total with chronic tularemia	13	10	Sick	Live	3	51	NA	No	0	Yes	125	NA	No
12			11	Sick	Live	3	22	NA	No	0	Yes	63	NA	No
13			12	Not Sick	Not sick	No Symptoms	NA	NA	Yes	3	No	NA	NA	No
14			13	Not Sick	Not sick	No Symptoms	2	NA	No	0	No	0	NA	No
15			14	Sick	Dead	5	24	28	Dead	Dead	Dead	Dead	NA	No
16			15	Not Sick	Not sick	No Symptoms	3	NA	No	0	No	0	NA	No
17			16	Not Sick	Not sick	No Symptoms	NA	NA	No	0	No	NA	NA	No
18			17	Not Sick	Not sick	No Symptoms	5	NA	No	0	No	0	NA	No
19			18	Sick	Dead	4	11	14	Dead	Dead	Dead	Dead	NA	No
20			19	Not Sick	Not sick	No Symptoms	2	NA	No	0	No	0	NA	No
21			20	Sick	Dead	3	10	12	Dead	Dead	Dead	Dead	NA	No
22			21	Not Sick	No Symptoms	No Symptoms	17	NA	No	0	Yes	34	NA	No
23			22	Sick	Dead	5	27	31	Dead	Dead	Dead	Dead	NA	No
24			23	Sick	Live	5	2	NA	No	0	Yes	4	NA	No
25			24	Not Sick	Not sick	No Symptoms	NA	NA	No	0	No	NA	NA	No
26			25	Not Sick	Not sick	No Symptoms	NA	NA	No	0	No	NA	NA	No
27			26	Sick	Dead	3	15	17	Dead	Dead	Dead	Dead	NA	No
28			27	Not Sick	Not sick	No Symptoms	NA	NA	Yes	3	No	NA	NA	No
29			28	Sick	Live	11	43	NA	No	0	Yes	93	NA	No
30			29	Not Sick	Not sick	No Symptoms	3	NA	No	0	No	0	NA	No

Input | Outputs | Graphs | Advanced User

Figure 4. Screen shot of "Outputs" tab.

The last tab available to users is the "Advanced User" tab. This tab allows users to change many of the modeling parameters including: the mortality rate in individuals who receive no MCM, the relapse rate after treatment, minimum days of work lost after treatment, and many others. As can be seen in Figure 5, each parameter on this tab has a user defined value and a recommended value. Users who wish to use the default values defined in this document should ensure that the values in the green "user defined value" column match those in the red "recommended values" column.

	A	B	C	D
1		**User defined**	**Recommended**	
2	Mortality rate in individuals who receive no MCM	75%	75%	
3	Additional length (in days) of incubation period in vaccinated individuals	1	1	
4	ID50 in vaccinated individuals	5607	5607	
5	Vaccine efficacy probit	0.5322	0.5322	
6	Work lost as a % of period of fever (Mean)	217%	217%	
7	Work lost as a % of period of fever (SD)	45%	45%	
8	Minimum days of work lost after treatment	14	14	
9	% of survivors who suffer from chronic tularemia	5%	5%	
10	Number of organisms that remain in body after PEP	5	5	
11	Relapse rate after treatment	2%	2%	
12	Additional days of work lost due to relapse	14	14	
13	% of individuals who receive PEP that lose work as a result of PEP	14%	14%	
14	% of those who lose work as a result of PEP that lose 1 day	35.71%	35.71%	
15	% of those who lose work as a result of PEP that lose 1 or 2 days	71.43%	71.43%	
16	% of those who lose work as a result of PEP that lose 1, 2, or 3 days	92.86%	92.86%	
17	% of those who lose work as a result of PEP that lose 1, 2, 3, or 7 days	100%	100%	
18				

Figure 5. Advanced user tab.

Modeling Assumptions and Parameters

Estimates of casualties following exposure to *F. tularensis* used in our medical countermeasure model are based on the values and functions describing the No MCM disease course parameters outlined by Curling et al.[7] These values and functions are summarized in the "No MCM Disease Course" section below. Our team developed the modeling parameters associated with MCM, including both MCM intended to prevent infection (vaccines and prophylactic antibiotics) and MCM that provide treatments for infected individuals (antibiotics). In the following sections, we outline the assumptions underlying the model, as well as the values or functions for the modeling parameters associated with each medical countermeasure, and the rationale for choosing each value.

[7] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

Assumptions: Base Case

Exposure

Although *F. tularensis* can cause disease via a vector (by penetrating the skin) or via ingestion (by penetrating the mucous membrane of the gastrointestinal tract), our model assumes exposure via inhalation, since this is the most likely route of infection on a battlefield.

Biovar

Since *F. tularensis* Type A is the most pathogenic of the *F. tularensis* subspecies (or biovars) we assume it is the biovar most likely to be used as a bioweapon; therefore, our model assumes exposure to Type A bacteria. This is the same assumption made for the No MCM model developed by Curling et al.[8]

Post-Exposure Prophylaxis (PEP)

We assume that individuals who receive PEP will receive oral ciprofloxacin or doxycycline and that the bacteria used in the attack have not been engineered to be resistant to these drugs.

Antibiotic Treatment

We assume that symptomatic individuals who receive antibiotics for treatment will be administered intravenous or intramuscular streptomycin or gentamicin and that the bacteria used in the attack have not been engineered to be resistant to these drugs. Since treatment occurs via injection and therefore under the supervision of medical personnel, we also assume that antibiotic treatment will be administered for the recommended duration of 10 days.[9]

Parameters

No MCM Disease Course

The parameters describing the no MCM disease course are taken from Curling et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia."[10] Our model of medical countermeasures is designed to merge with this previously established model of the disease with no MCM.

Curling et al. report an ID_{50} (median infectious dose) for inhaled *F. tularensis* of 10 organisms and a mortality rate of 75% when individuals are given no MCM. Furthermore, they define a dose-dependent incubation period (typically of less than one week) that precedes the onset of symptoms. The incubation period is followed by Stage 1 symptoms, which include high fever, headache, chills, sore throat, myalgia, and chest pain. According to Curling et al., survivors who receive no MCM experience two additional

[8] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

[9] Dennis DT et al. "Consensus Statement: Tularemia as a Biological Weapon: Medical and Public Health Management." *JAMA.* **285** (21). 2001.

[10] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

stages of the disease. Stage 2 includes the signs and symptoms seen in Stage 1 plus mild pneumonia.[11] In Stage 3, recovery, survivors experience malaise and severe weakness.[12,13] Our model encompasses the recovery period as part of our loss-of-work parameter (see "Days of work lost due to illness in an individual who recovers" section). In non-survivors, Stage 2 is more serious than in survivors and includes severe pneumonia and respiratory distress followed by death;[14] thus, non-survivors never reach Stage 3, recovery. Below, we summarize the no MCM modeling parameters established by Curling et al. in "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents": infectivity, length of the disease course, and mortality rate.[15]

Infectivity

The infectivity parameter established by Curling et al.[16] operates as a function of dose, where the likelihood of infection increases as the inhaled dose increases. The schematic shown below (Figure 6) illustrates the data that influence this modeling parameter.

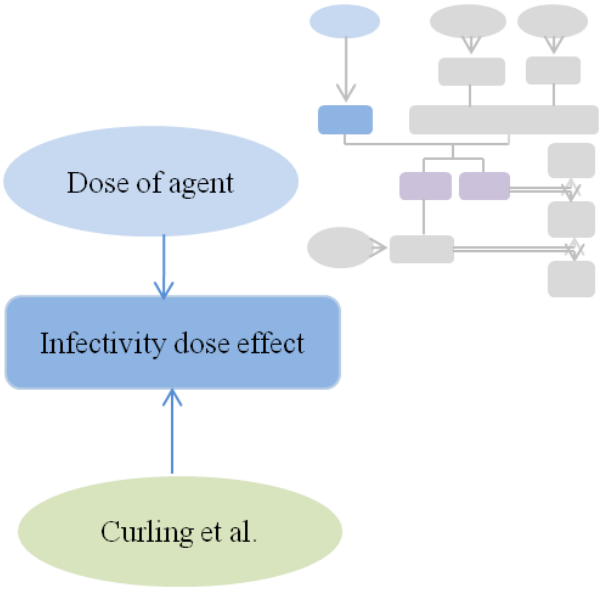


Figure 6. Modeling scheme for infectivity. The light blue oval indicates the user input, the dark blue rectangle indicates the modeling parameter calculations and the green oval indicates data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or function:

Probability of developing symptoms is a lognormal distribution:

ID_{50}: 10 organisms

Probit slope: 1.90 probits/log(dose)

[11] Stage 1 symptoms in all individuals and Stage 2 symptoms in survivors are defined by Curling et al as "Severity Level 3 - Severe."

[12] Stage 3 symptoms are defined by Curling et al as "Severity Level 2 - Moderate."

[13] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

[14] Stage 2 symptoms in non-survivors are defined by Curling et al as "Severity Level 4-Very Severe".

[15] In a few circumstances the parameters established by Curling et al were adjusted to accommodate our medical countermeasure model. All adjustments are described in this document.

[16] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

Individuals for Whom this Parameter Applies:

The infectivity parameter is applied to all individuals unless it is modified or replaced by another parameter (like the "Probability of developing symptoms after vaccination" parameter).

Rationale:

Taken from Curling et al.[17]

Length of Incubation Period

The length of the incubation period is dose dependent; therefore, individuals that inhale large doses of agent have a shorter average incubation period than those that inhale small doses. The schematic shown below (Figure 7) illustrates the data that influence the length of the incubation period.

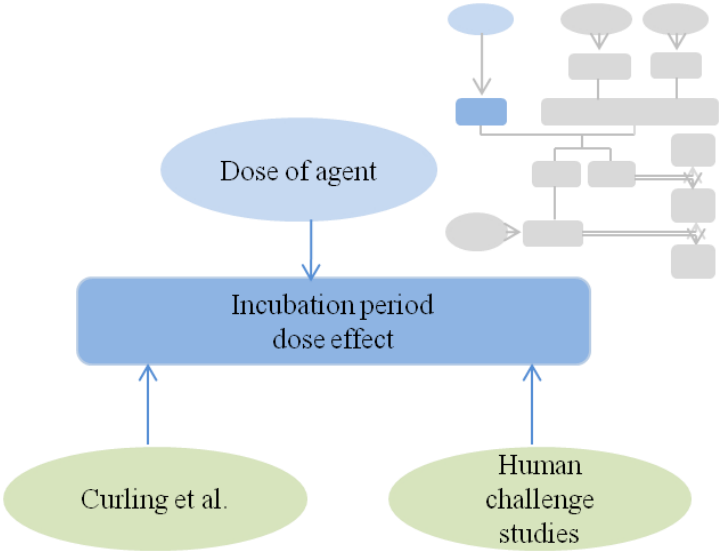


Figure 7. Modeling scheme for incubation period. The light blue oval indicates the user input, the dark blue rectangle indicates the modeling parameter calculations and green ovals indicate data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or function:

Length of the incubation period (t_0) is a normal distribution with mean and standard deviation are:

For doses $<10^5$, Mean = $6.5380 - 0.8207 logD_0$
Standard deviation: 0.73 days

For doses 10^5-10^7,Mean = $10.9563 - 2.5886 logD_0 + 0.1763 (logD_0)^2$
Standard deviation: 0.73 days

For doses $>10^7$, Mean = 1.5

[17] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

Standard deviation: 0.73 days

Where:
t_0 = length of incubation period in days
D_0 = dose of organisms inhaled
$t_0 \geq 1.5$ days

Individuals for Whom this Parameter Applies:

The "Length of the Incubation Period" parameter is applied to all individuals who develop symptoms, but may be modified or replaced by other parameters described below (like the "Vaccine effect on incubation period" parameter). The length applied to each individual is dependent on their input dose.

Rationale:

The dose dependent incubation periods used in our model were taken from Curling et al.; however, no standard deviations were reported.[18] Curling et al. indicate that the incubation periods were taken from the "Consequence Analytic Tools for NBC Operations," which established the periods using data from 96 unpublished cases of tularemia as well as 16 cases described by Saslaw et al. [19] Although we were unable to obtain the raw data from the 96 unpublished cases of tularemia, the Saslaw data set was used to estimate standard deviations for doses of approximately 15, 25, and 50 organisms (see Appendix 1). The resulting standard deviations were 0.75, 0.89, and 0.55 days. By averaging the three standard deviations, we arrived at the standard deviation that we used for our model, 0.73 days. Per Curling et al., we ensure that the incubation period calculated for an individual is never less than 1.5 days. It is important to note that the standard deviation was calculated from the limited data set available from Saslaw et al, and are assumed to be applicable to the higher exposures described in the 96 unpublished cases referenced by "Consequence Analytic Tools for NBC Operations." If the entire unpublished dataset becomes available, this standard deviation could be adjusted.

Length of Stage 1

The average Stage 1 symptomatic period (the initial febrile period of the disease) was established by Curling et al.[20] The schematic below (Figure 8) illustrates the data that influence this modeling parameter.

[18] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.
[19] Saslaw S et al. "Tularemia vaccine study: II. Respiratory challenge." *Archives of internal medicine*. **107**(5). 1961.
[20] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

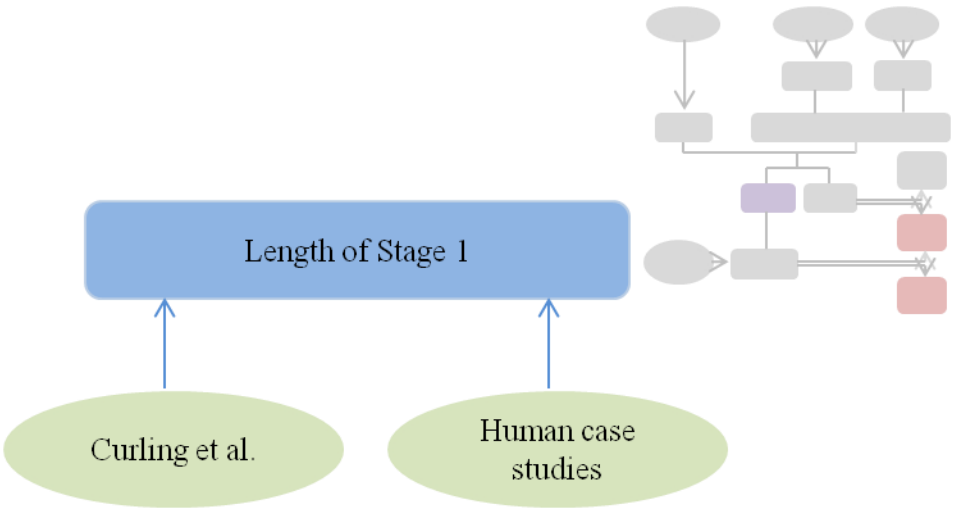


Figure 8. Modeling scheme for length of Stage 1. The dark blue rectangle indicates the modeling parameter calculation and the green ovals indicate data used to establish this parameter. The inset image shows how the parts of the larger Figure 1 modeling scheme are affected by this parameter.

Value or function:

Length of Stage 1 in individuals who would die without MCM is a normal distribution:

Mean: 9 days
Standard deviation: 2 days

Length of Stage 1 in individuals who would live without MCM is a normal distribution:

Mean: 12 days
Standard deviation: 2.8 days

Individuals for Whom this Parameter Applies:

The "Length of Stage 1" parameter is applied to all symptomatic individuals. The length that is applied to each individual is dependent on whether that individual would have lived or died if they had not received MCM. The duration of the symptomatic stages may be modified or replaced by other parameters described below (like the "Effect of disease severity on length of disease course in vaccinated individuals.")

Rationale:

The length of Stage 1 was taken from Curling et al.; however, no standard deviation was reported.[21] Curling et al. indicate that the Stage 1 period was established using data from a review by Stuart and Pullen. [22] The raw data from this report were used to estimate a standard deviation for Stage 1 in individuals who received no MCM that lived and individuals who received no MCM that died (see Appendix 2 for the raw data used to estimate the standard deviation).

[21] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

[22] Stuart BM and Pullen RL. "Tularemic pneumonia. Review of American literature and report of 15 additional cases." *Am Med Sci.* **210**(2). 1945.

Length of Stage 2

The average Stage 2 symptomatic period (the pneumonic stage of disease) was established by Curling et al.[23] The schematic shown below (Figure 9) illustrates the data that influence this modeling parameter.

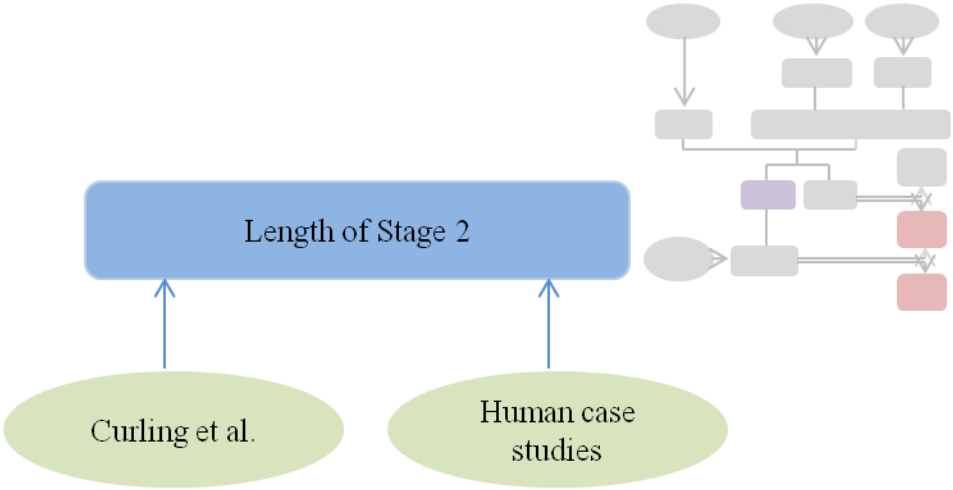


Figure 9. Modeling scheme for length of Stage 2. The dark blue rectangle indicates the modeling parameter calculations and the green ovals indicate data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or function:

Length of Stage 2 in people who would die without MCM is a normal distribution*:

Mean: 6 days

Standard deviation: 6.4 days

*Regardless of model calculations, if the length of Stage 2 is less than one day our model reports the minimum length for Stage 2, one day

Length of Stage 2 in people who would live without MCM is a normal distribution:

Mean: 28 days

Standard deviation: 7.8 days

Individuals for Whom this Parameter Applies:

The "Length of Stage 2" parameter is applied to all symptomatic individuals; however, the duration of the symptomatic stages may be modified or replaced by other parameters described below (like the "Effect of disease severity on length of disease course in vaccinated individuals.") The length that is applied to each individual is dependent on whether that individual would live or die without MCM.

Rationale:

The length of Stage 2 was taken from Curling et al.; however, no standard deviation was reported.[24] Curling et al. indicate that the Stage 2 period was established using data from a report

[23] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

[24] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

by Stuart and Pullen.[25] The raw data from this report were used to estimate a standard deviation for Stage 2 in individuals that lived and individuals that died (see Appendix 2 for more information).

Duration of Fever

The duration of fever was established based on the description of the no MCM disease course developed by Curling et al, and is dependent on the outcomes for the length of Stage 1 and Stage 2.[26] The schematic shown below (Figure 10) illustrates the data that influence this modeling parameter.

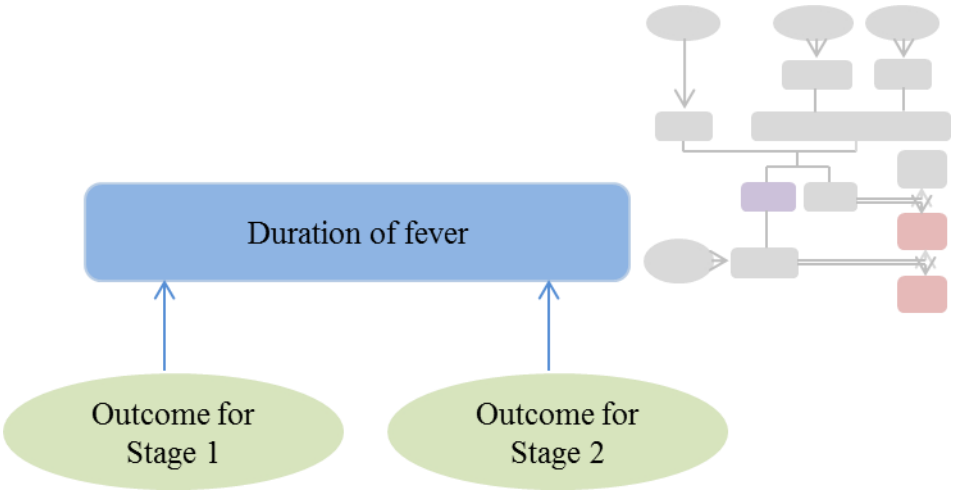


Figure 10. Modeling scheme for the duration of fever. The dark blue rectangle indicates the modeling parameter calculation and green ovals indicate data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or Function:

$F = St_1 + St_2$

Where:
F = Period of fever
St_1 = Length of Stage 1
St_2 = Length of Stage 2

Individuals for Whom this Parameter Applies:

The "Duration of Fever" parameter applies to all symptomatic individuals, but may be modified or replaced by other parameters described below (like the "Duration of fever in a treated individual who recovers").

Rationale:

Curling et al indicate that fever begins at the onset of symptomatic Stage 1 and continues for the duration of Stage 2.[27] This assertion is supported by case studies (Table A-12 in Appendix 6) that

[25] Stuart BM and Pullen RL. "Tularemic pneumonia. Review of American literature and report of 15 additional cases." *Am Med Sci.* **210**(2). 1945.

[26] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

indicate that individuals with tularemia typically have a fever that exceeds 103°F.[28] Therefore in our model, the no MCM duration of fever is equal to the duration of Stage 1 plus the duration of Stage 2.

Time of Death

The time of death was established based on the model developed by Curling et al, and is dependent on the outcomes for the incubation period, the duration of Stage 1, and the duration of Stage 2.[29] The schematic shown below (Figure 11) illustrates the data that influence this modeling parameter.

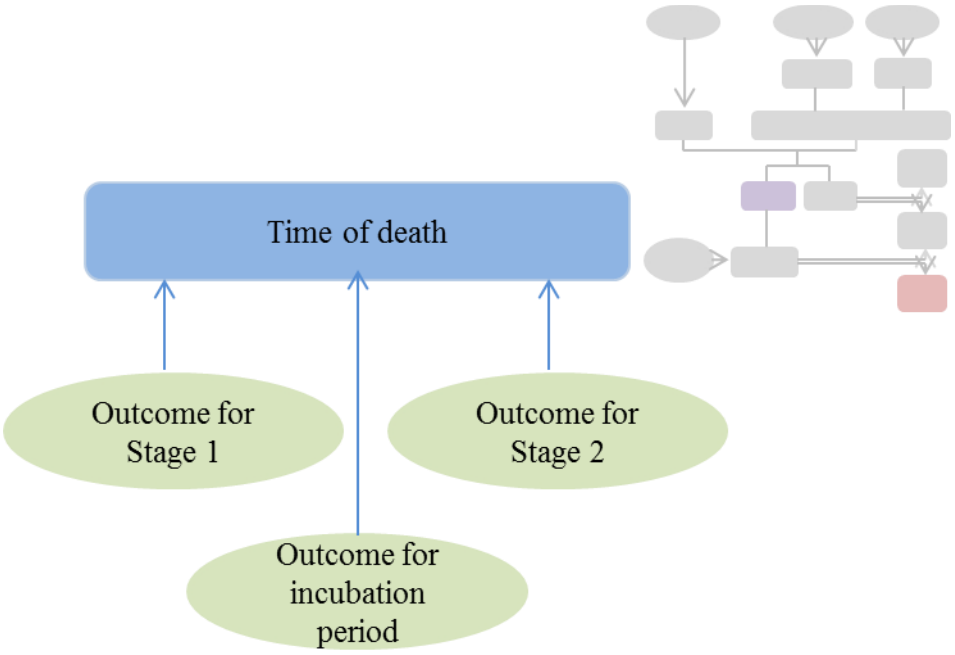


Figure 11. Modeling scheme for the time of death. The dark blue rectangle indicates the modeling parameter calculation and green ovals indicate data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or Function:

$TTD = t_0 + St_1 + St_2$

Where:

TTD = Time to death after exposure

t_0 = Length of the incubation period

St_1 = Length of Stage 1

St_2 = Length of Stage 2

Individuals for Whom this Parameter Applies:

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[27] Curling, C et al. "Parameters for Estimation of Casualties from Exposure to Selected Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia. Volume I: DRAFT 02/07/2011. Tularemia Extract." Institute for Defense Analysis (IDA) Document D-4132, November 2010.

[28] Table 3-1 from: Anno et al. Consequence Analytic Tools for NBC Operations, Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever. Defense Special Weapons Agency. 1998

[29] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

The "Time of Death" parameter applies to all symptomatic individuals who die. Note that parameters that affect the length of the incubation period or the symptomatic periods (for example, the "Vaccine effect on incubation period" parameter) will also affect the time to death.

Rationale:

Curling et al indicate that individuals who die without receiving any MCM experience symptomatic Stage 1 and Stage 2, but never reach the recovery stage (which is described in detail below).[30] Therefore, in our model the time of death is equal to the duration of the incubation period plus the duration of the symptomatic periods (Stage 1 and Stage 2).

Mortality Rate in Infected Individuals with No MCM

The mortality rate parameter was established by Curling et al.[31] The schematic shown below (Figure 12) illustrates the data that influence this modeling parameter.

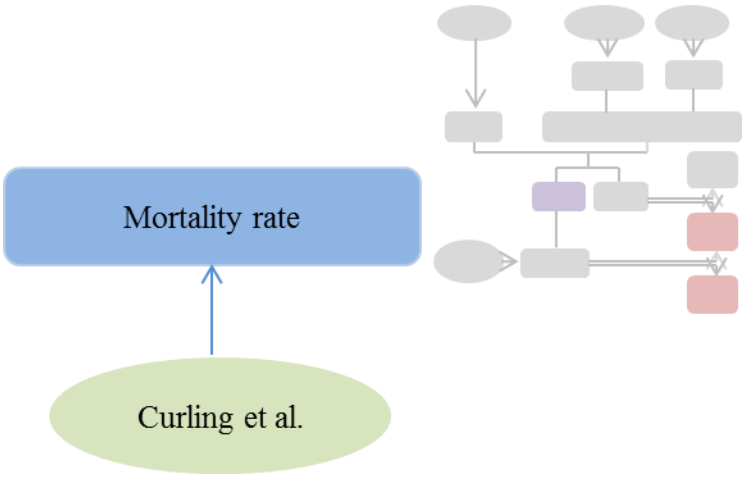

Figure 12. Modeling scheme for mortality rate. The dark blue rectangle indicates the modeling parameter calculation and green ovals indicate data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or Function:

No MCM Mortality rate = 75%

Individuals for Whom this Parameter Applies:

The mortality rate parameter is applied to all symptomatic individuals but may be modified by other parameters (like the antibiotic treatment parameters).

Rationale:

The mortality rate for individuals who receive no MCM was taken from Curling et al. [32]

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[30] Curling, C et al. "Parameters for Estimation of Casualties from Exposure to Selected Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia. Volume I: DRAFT 02/07/2011. Tularemia Extract." Institute for Defense Analysis (IDA) Document D-4132, November 2010.

[31] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

[32] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

F. tularensis Vaccine

The tularemia live vaccine strain (LVS) was developed in 1956 and was awarded investigational new drug status in the early 1960s.[33,34] LVS was used to vaccinate the staff of the United States Army Medical Research Institute for Infectious Diseases (USAMRIID) involved in the tularemia program and resulted in a significant decrease in laboratory-acquired tularemia rates; however, the vaccine is currently unlicensed and unavailable.[35,36]

Unlike many vaccines against select agents, the efficacy of LVS has been tested in challenge studies with human volunteers.[37,38,39,40] These studies were performed by administering the vaccine orally, via aerosol, or intranasally as well as through its typical route of delivery, scarification. Unfortunately, these tests indicate that LVS has several drawbacks.[41,42,43,44] Vaccinated individuals typically develop lesions at the site of scarification and about half display regional axillary adenopathy (swollen lymph nodes in the armpit).[45] Moreover, a study by Hornick and Eigelsbach shows that although protection does not appear to be linked to the time between vaccination and challenge, the protection afforded by LVS is incomplete.[46]

Below we outline the vaccine-related parameters used in our model and the rationale behind choosing each parameter. Vaccine parameters include pre-exposure efficacy, the effect of vaccination on the incubation period, and the effect of vaccination on the severity of disease. Note that all our vaccine parameters were established using data from individuals who were vaccinated via scarification.

Probability of Developing Symptoms After Vaccination

The "Probability of developing symptoms after vaccination" parameter was established using data from human vaccination challenge studies conducted in volunteers (detailed below). The schematic shown below (Figure 13) illustrates the data that were used to establish the "Probability of developing symptoms after vaccination" modeling parameter.

---

33 Conlan J and Oyston P. "Vaccines against *Francisella tularensis*." *Annals of the New York Academy of Sciences*. **1105**. 2007.

34 Pechous R et al. "Working toward the future: insights into *Francisella tularensis* pathogenesis and vaccine development." *Microbiology and Molecular Biology Reviews*, **73**(4). 2009.

35 Conlan J and Oyston P. "Vaccines against *Francisella tularensis*." *Annals of the New York Academy of Sciences*. **1105**. 2007.

36 Pechous R et al. "Working toward the future: insights into *Francisella tularensis* pathogenesis and vaccine development." *Microbiology and Molecular Biology Reviews*, **73**(4). 2009.

37 Hornick R and Eigelsbach H. "Aerogenic immunization of man with live Tularemia vaccine." *Microbiology and Molecular Biology Reviews*. **30**(3).1966.

38 Saslaw S et al. "Tularemia vaccine study: II. Respiratory challenge." *Archives of internal medicine*. **107**(5). 1961.

39 McCrumb Jr F." Aerosol infection of man with *Pasteurella tularensis*." *Microbiology and Molecular Biology Reviews*. **25**(3). 1961.

40 Pekarek R et al. "The effects of *Francisella tularensis* infection on iron metabolism in man." *The American Journal of the Medical Sciences*. **258**(1). 1969.

41 KuoLee R. et al. "Oral immunization of mice with the live vaccine strain (LVS) of *Francisella tularensis* protects mice against respiratory challenge with virulent type A *F. tularensis*." *Vaccine*. **25**(19). 2007.

42 Hornick R and Eigelsbach H. "Aerogenic immunization of man with live Tularemia vaccine." *Microbiology and Molecular Biology Reviews*. **30**(3).1966.

43 Oyston PCF and Quarry JE. "Tularemia vaccine: past, present and future." *Antonie van Leeuwenhoek*. **87**(4). 2005.

44 Barrett A. and Stanberry L. *Vaccines for biodefense and emerging and neglected diseases*. Academic Press. 2009.

45 Saslaw S et al. "Tularemia vaccine study: II. Respiratory challenge." *Archives of internal medicine*. **107**(5). 1961.

46 Hornick RB and Eigelsbach HT. "Aerogenic Immunization of Man with Live Tularemia Vaccine." *Bacteriological Reviews*. **30**(3). 1966.

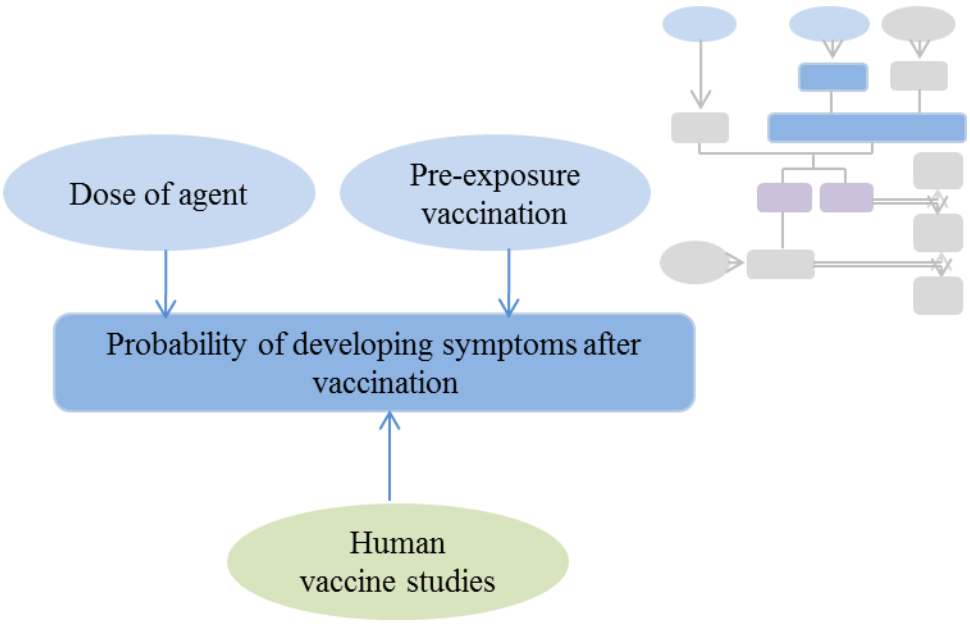

Figure 13. Modeling scheme for probability of developing symptoms after vaccination. Light blue ovals indicate user inputs, the dark blue rectangle indicates the modeling parameter calculations, and the green oval indicates data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or Function:

The probability of developing symptoms after vaccination is a lognormal distribution:

ID_{50}: 5607 organisms

Probit slope: 0.5322 probits/log dose

Individuals for Whom this Parameter Applies:

The "Probability of developing symptoms after vaccination" is applied to vaccinated individuals only. This parameter is used to calculate the chance that a vaccinated individual will develop symptoms.

Rationale:

A series of tularemia vaccine challenge studies were published in the 1960s (detailed in Appendix 3). These studies involved vaccinating human volunteers with a live attenuated strain of *F. tularensis* or with chemically fractionated cell-wall antigen from the bacteria. Some volunteers were vaccinated via acupuncture or scarification while others were vaccinated via the respiratory route. Since the vaccine that has been used in the United States in the past is an attenuated live strain administered via scarification, we considered only studies with these characteristics when developing our parameter. The number of boosters and the time interval between the last booster and exposure do not appear to have an effect on the chance of developing disease or on the severity of symptoms in those who develop disease following vaccination. Our model, therefore, offers only two vaccination inputs: vaccinated or unvaccinated.

Figure 14, which was developed using the data described above, illustrates that the efficacy of the vaccine decreases as the dose of inhaled agent increases. Using a lognormal distribution with an ID_{50} of 5607 and a probit slope of 0.5322 probits/log dose, our model predicts what proportion of

vaccinated individuals develop illness following exposure to varying doses of agent (see Appendix 3 for information on each study used in our analysis).[47,48,49,50]

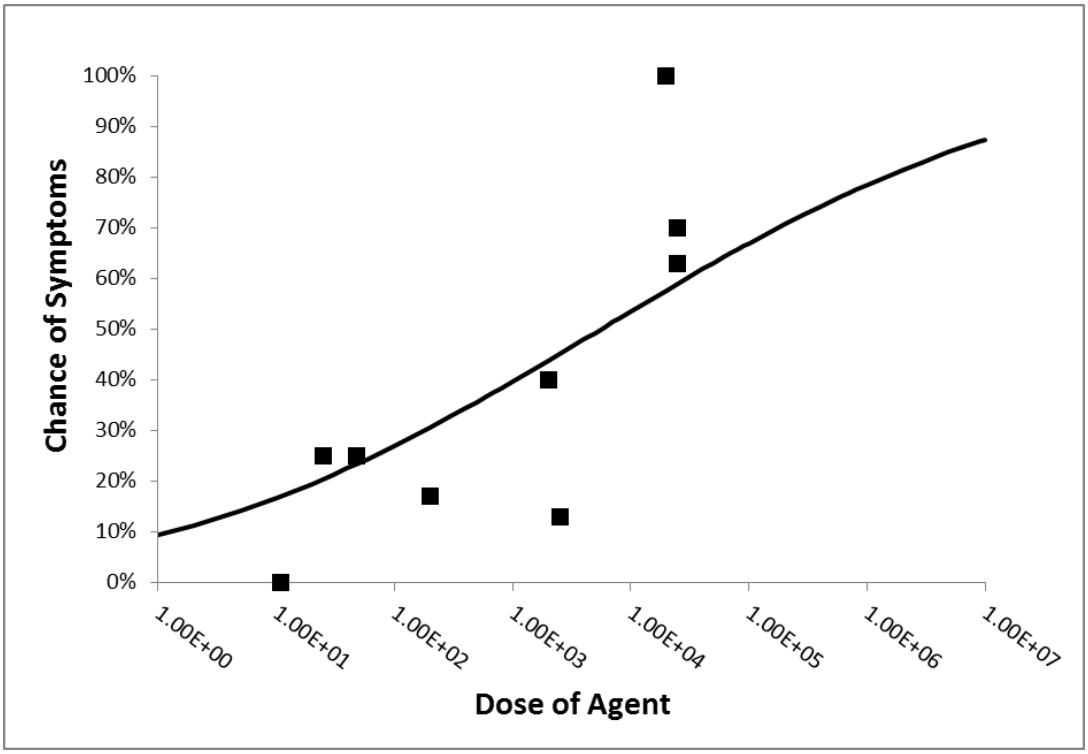

Figure 14. Percentage of vaccinated individuals that developed illness following exposure to varying doses of agent. Black squares represent the data points from tularemia challenge studies that were used to create the curve and the black line shows the equation described by a lognormal distribution with an ID_{50} of 5607 and a probit slope of 0.5322 probits/log dose.

Vaccine Effect on Incubation Period

The parameter describing the effect of *F. tularensis* vaccination on the incubation period is based on data from human volunteers who developed symptoms despite vaccination (studies detailed below). The schematic shown below (Figure 15) illustrates the data that were used to establish this modeling parameter.

47 Hornick R and Eigelsbach H. "Aerogenic immunization of man with live Tularemia vaccine." *Microbiology and Molecular Biology Reviews*. **30**(3).1966.

48 Saslaw S et al. "Tularemia vaccine study: II. Respiratory challenge." *Archives of internal medicine*. **107**(5). 1961.

49 McCrumb Jr F." Aerosol infection of man with *Pasteurella tularensis*." *Microbiology and Molecular Biology Reviews*. **25**(3). 1961.

50 Pekarek R et al. "The effects of *Francisella tularensis* infection on iron metabolism in man." *The American Journal of the Medical Sciences*. **258**(1). 1969.

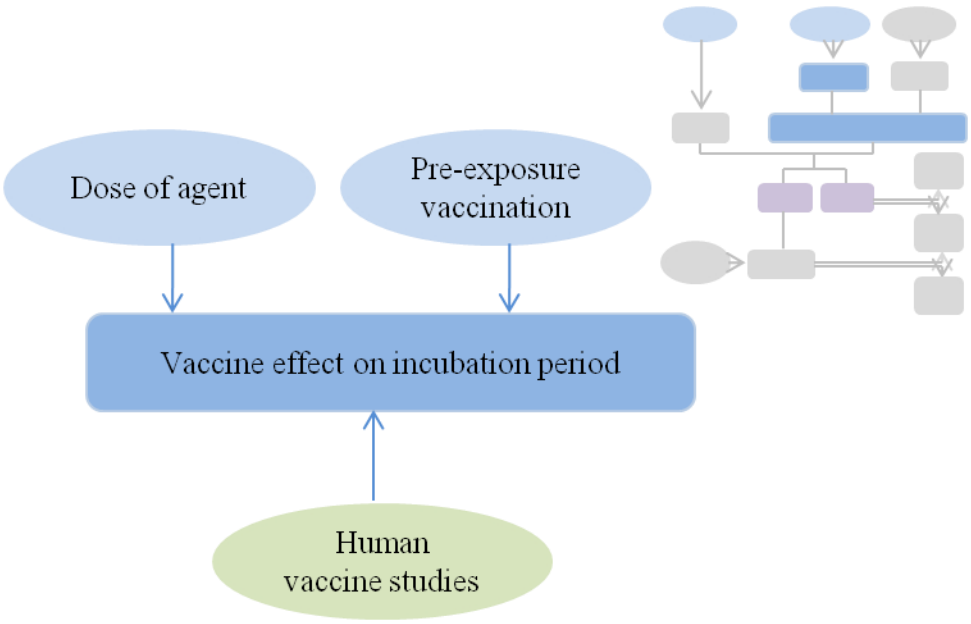

Figure 15. Modeling scheme for the effect of pre-exposure vaccine on the length of the incubation period. Light blue ovals indicate user inputs, the dark blue rectangle indicates the modeling parameter calculations and the green oval indicates data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or Function:

$t_{0(vaccinated)} = t_0 + 1\ day$

Where:

$t_{0(vaccinated)}$ = the incubation period in vaccinated individuals

t_0 = incubation calculation for unvaccinated individuals (as described in "Length of Incubation Period")

Individuals for Whom this Parameter Applies:

The "Vaccine effect on incubation period" parameter modifies the length of the incubation period for all vaccinated individuals who develop symptoms by the value described above. This parameter may be modified by other parameters (like the "Timing of post-PEP disease course" parameter).

Rationale:

Hornick and Eigelsback report that the average incubation period in vaccinated individuals is one day longer than in unvaccinated individuals.[51] Although the data supporting this assertion comes from high exposure doses, individuals that develop symptoms after vaccination are more likely to have received a high dose than a low dose (as described in the "Probability of developing symptoms after vaccination" section.) Given that we found no additional data relating to the effect of vaccination on the length of the incubation period after low-dose exposure, we assume that the one-day increase in the incubation period is applicable to all vaccinated individuals that develop symptoms.

[51] Hornick RB and Eigelsbach HT. "Aerogenic Immunization of Man with Live Tularemia Vaccine." *Bacteriological Reviews*. **30**(3). 1966

Vaccine Effect on Disease Severity and Outcome

Data from human volunteers (detailed in Appendix 3) show that the severity of disease in vaccinated individuals who develop symptoms is often milder than a typical tularemia infection. These data also show that these milder infections come in two forms, which we define as Type I (the mildest form of the disease) and Type II (more severe than Type I, but milder than the typical form of the disease). The human data (described below) also show that individuals with either mild type of illness have a decreased risk of death when compared to those with a typical form of the disease. The schematic shown below (Figure 16) illustrates the data that were used to establish the parameter describing the effect of the vaccine on the disease severity and outcome.

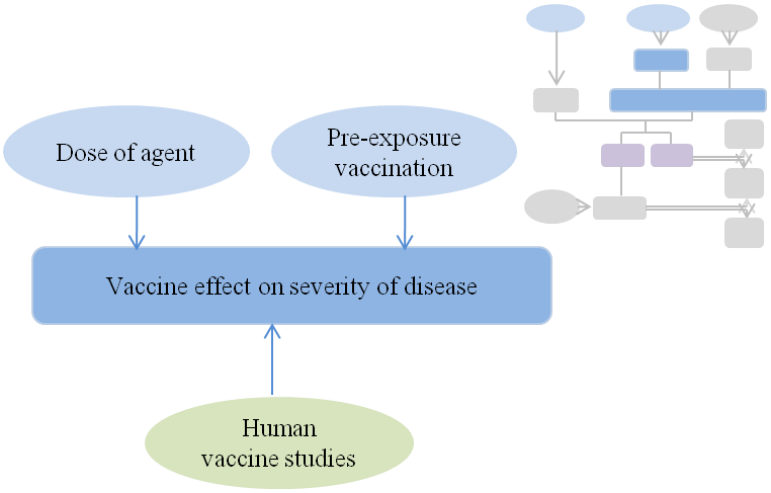

Figure 16. Modeling scheme for the effect of vaccine on disease severity and outcome. Light blue ovals indicate user inputs, the dark blue rectangle indicates the modeling parameter calculation, and the green oval indicates data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or function:

Vaccinated individuals who develop symptoms may develop a mild form of the disease or a typical form of the disease. The following equations describe the percentage of vaccinated symptomatic individuals whose disease severity (Z) is mild or typical. For individuals calculated to having a mild form of the disease an additional calculation is performed to determine if the disease is mild Type I, or mild Type II (see description below).

Percentage of symptomatic vaccinated individuals with any form of mild disease

If $(1.6980 - 0.2948\log(D_0)) < 0.00$, $Z_{mild} = 0\%$

If $(1.6980 - 0.2948\log(D_0)) > 1.00$, $Z_{mild} = 100\%$

Otherwise: $Z_{mild} = (1.6980 - 0.2948\log(D_0))$

Where:

D_o is the dose of agent

Z_{mild} = percentage of symptomatic individuals who develop any type of mild illness

Percentage of all symptomatic individuals that have Mild Type I

If $(1.651 - 0.50 * \log(D_0)) * Z_{mild} < 0.00$, $Z_{MI} = 0\%$

If $(1.651 - 0.50 * \log(D_0)) * Z_{mild} > 1$, $Z_{MI} = 100\%$
Otherwise: $Z_{MI} = (1.651 - 0.50 * \log(D_0)) * Z_{mild}$

Where:
D_o is the dose of agent
Z_{mild} = percentage of all symptomatic individuals who develop any type of mild illness
Z_{MI} = percentage of all symptomatic individuals who develop a mild Type I form of the disease

Percentage of all symptomatic individuals that have Mild Type II
$Z_{MII} = Z_{mild} - Z_{MI}$

Where:
Z_{mild} = percentage of all symptomatic individuals who develop any type of mild illness
Z_{MI} = percentage of all symptomatic individuals who develop a mild Type I form of the disease
Z_{MII} = percentage of all symptomatic individuals who develop a mild Type II form of the disease

Percentage of symptomatic vaccinated individuals with the typical form of the disease.
$Z_T = 1 - Z_{mild}$

Where:
Z_T = percentage of symptomatic individuals who develop a typical form of the disease
Z_{mild} = percentage of symptomatic individuals who develop any type of mild illness

Mortality outcome in symptomatic vaccinated individuals:
Mild Type I: Mortality rate = 0%
Mild Type II: Mortality rate = 0 %
Typical: Mortality rate = 75%

Individuals for Whom this Parameter Applies:

The "Vaccine effect on disease severity and outcome" parameter determines the disease severity and mortality outcome in all vaccinated individuals who develop symptoms.

Rationale:

Human vaccine studies (detailed in Appendix 3) show that some vaccinated individuals who develop symptoms experience a milder form of the disease than those who are unvaccinated. As with the overall efficacy of the vaccine, this effect appears to be dose dependent. Data from McCrumb, [52] Pekerek et al,[53] and Hornick and Eigelsbach[54] were analyzed to predict what percent of vaccinated symptomatic individuals develop a mild (rather than typical) form of disease at varying doses.

While the three studies listed above each reported mild illness differently, taken together they show a significant relationship between dose and severity of disease in symptomatic, vaccinated

[52] McCrumb FR. "Aerosol Infection of Man with *Pasteurella Tularensis." Bacteriol Rev*. **25**(3). 1961.
[53] Pekarek RS et al. "The Effects of *Francisella Tularensis* Infection on Iron Metabolism in Man." *The American Journal of the Medical Sciences.* **258**(1). 1969.
[54] Hornick RB and Eigelsbach HT. "Aerogenic Immunization of Man with Live Tularemia Vaccine." *Bacteriological Reviews*. **30**(3). 1966.

individuals. The equation $Z_{mild} = (1.6980 - 0.2948\log(D_0))$ describes the percent of individuals (Z_{mild}) who develop a mild (rather than a typical) form of tularemia as a function of dose. The details of the data from each study and the derivation of this equation are described in Appendix 3.

In addition to distinguishing between mild and typical disease, one author went on to describe multiple types of mild illness. In his paper "Aerosol Infection of Man with *Pasteurella tularensis,"* McCrumb describes two distinct types of mild disease. The least severe form, which we refer to as mild Type I, is characterized by a symptomatic period that is only 24-48 hours. The other mild illness, which we refer to as mild Type II, is characterized by symptoms that persist more than 48 hours, but are still mild when compared to the typical illness. We include both types of mild illness in our model in order to more accurately represent the possible range of the symptomatic period.

Just as the proportion of people who develop mild versus typical illness is dose-dependent, so too is the percentage of people who develop Type I versus Type II mild disease. Using the raw data from McCrumb, we developed an equation to describe the relationship between dose and the proportion of patients with mild disease who develop Type I rather than Type II mild disease. Appendix 3 describes both the McCrumb study and the derived equations. The proportion of all symptomatic patients who develop mild Type I (Z_{MI}) is given by the equation $Z_{MI} = (1.651 - 0.50 * \log(D_0)) * Z_{mild}$ and the proportion of patients who develop mild Type II is given by the equation $Z_{MII} = Z_{mild} - Z_{MI}$ where Z_{mild} is as defined above and D_0 is the inhaled dose. Therefore, the proportion of patients who develop typical tularemia (Z_T) is given by the equation: $Z_T = 1 - Z_{mild}$. Figure 17 below shows the proportion of patients with mild Type I, mild Type II and typical tularemia as a function of dose.

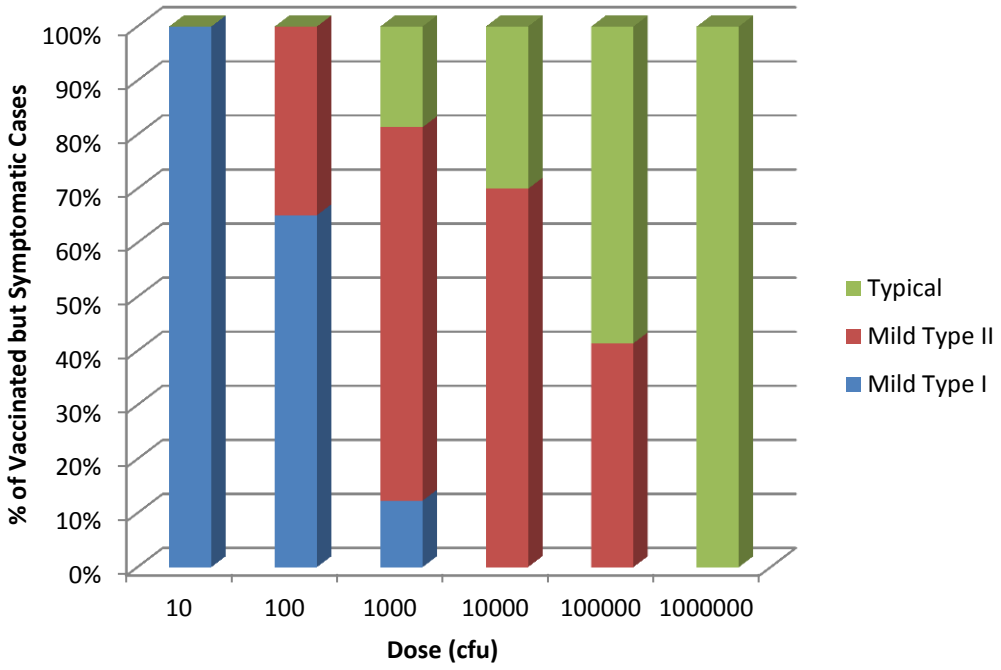

Figure 17. The severity of illness after symptom onset in vaccinated individuals is dependent on dose. Low doses are more likely to result in a milder disease, while very high doses are more likely to result in a typical disease.

Although mild illness is described differently by different authors, Hornick and Eigelbach (who use the broadest definition of "mild") reported that individuals with mild disease did not require antibiotics. Therefore, our model assumes that all individuals who experience either type of mild disease will survive even in the absence of antibiotics. In comparison, the typical disease has a mortality rate of 75% in the absence of antibiotics, as reported by Curling et al.[55] The symptomatic period for mild Type I and mild Type II illness is discussed further in the following section.

Effect of Disease Severity on Length of Disease Course in Vaccinated Individuals

The parameter describing the effect of disease severity on the length of the no MCM disease course in vaccinated individuals who develop disease was established using human case studies (described below). The schematic shown below (Figure 18) illustrates the data that influence this modeling parameter.

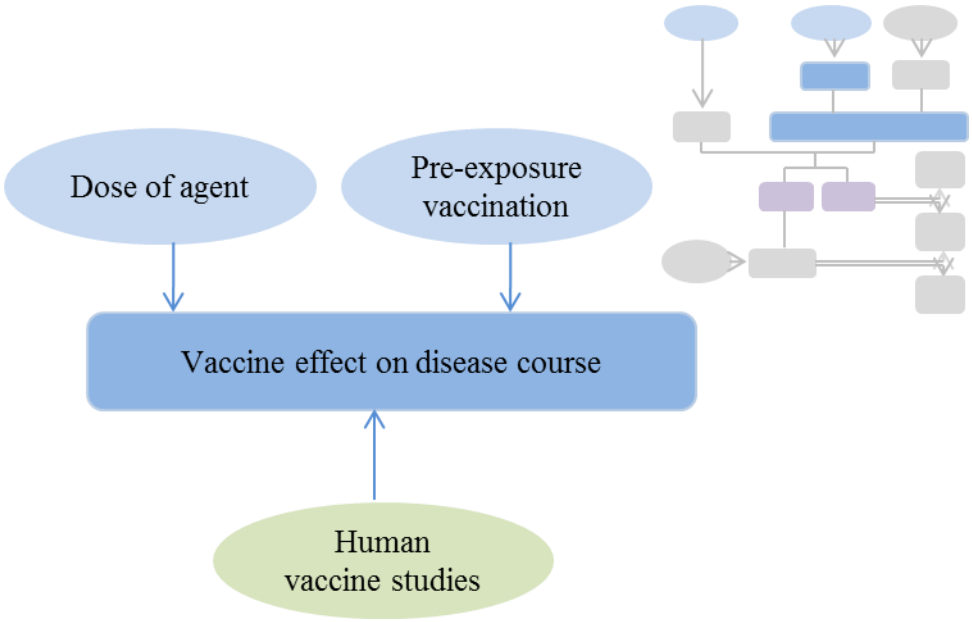

Figure 18. Modeling scheme for the effect of disease severity on the disease course. Light blue ovals indicate user inputs, the blue rectangle indicates the modeling parameter calculations, and the green oval indicates data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or function:

Individuals with Mild Type I Illness:

Length of incubation period:

Equal to the length of the incubation period in an individual who experiences the typical form of the disease

Length of Stage 1(St_1) is a normal distribution*:

Mean: 1.5 days

Standard Deviation: 0.5 days

[55] Curling, C et al. "Parameters for Estimation of Casualties from Exposure to Selected Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia. Volume I: DRAFT 02/07/2011. Tularemia Extract." Institute for Defense Analysis (IDA) Document D-4132, November 2010.

*Regardless of model calculations, the model output is never less than the minimum length of Stage 1 (one day)

Length of Stage 2 (St_2)

Stage 2 is not experienced in individuals with Mild Type I Illness

Individuals with Mild Type II Illness:

Length of incubation period:

Equal to the length of the incubation period in an individual who experiences the typical form of the disease

Length of Stage 1 (St_1):

In individuals with Mild Type II illness, Stage 1 is calculated to be the same length as Stage 1 (St_1) in an individual who experiences the typical form of the disease

Length of Stage 2:

Stage 2 is not experienced in individuals with Mild Type II illness

Individuals with Typical Illness:

The length of the incubation period (t_0), Stage 1 (St_1) and Stage 2 (St_2) are as described in the "No MCM Disease Course" section

Individuals for Whom this Parameter Applies:

The "Effect of disease severity on length of disease course in vaccinated individuals" parameter modifies the durations of Stage 1 and Stage 2 (and thus the duration of fever) in vaccinated individuals that develop mild symptoms. The duration applied to each individual is dependent on whether that individual develops Mild Type I, Mild Type II, or Typical illness.

Rationale:

In addition to not requiring treatment, individuals experiencing mild disease had a shorter symptomatic period than those experiencing typical symptoms. McCrumb indicates that mild Type I tularemia (as defined in the "Vaccine effect on disease severity and outcome" parameter) is characterized by a symptomatic period that is only 24-48 hours.[56] Therefore, our model assumes that those with this very mild form of the disease experience only Stage 1 symptoms and that these symptoms last an average of 1.5 days. McCrumb also reports that those with mild Type II illness (as defined previously) develop symptoms that persist longer than 48 hours, but which are still mild when compared to the typical illness. Though the exact length of the mild Type II illness is not given, we hypothesize that those with mild Type II illness will never experience Stage 2 symptoms (the more severe symptoms) since mild illness does not require antibiotics. Thus, our model assumes that individuals with mild Type II disease recover after Stage 1. The symptomatic period in vaccinated individuals experiencing typical illness is the same as predicted by Curling et al[57] (described in the "No MCM Disease Course" section). We found no information to support any change in the length of the incubation period in individuals with mild illness; therefore the incubation period calculation is the same as the calculation in survivors with no MCM.

[56] McCrumb FR. "Aerosol Infection of Man with *Pasteurella Tularensis." Bacteriol Rev*. **25**(3). 1961.

[57] Curling, C et al. "Parameters for Estimation of Casualties from Exposure to Selected Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia. Volume I: DRAFT 02/07/2011. Tularemia Extract." Institute for Defense Analysis (IDA) Document D-4132, November 2010.

Post Exposure Prophylaxis

Following exposure to *F. tularensis*, the Centers for Disease Control and Prevention (CDC) recommends that children and adults receive oral ciprofloxacin or doxycycline for post-exposure prophylaxis (PEP). The recommended dose of oral ciprofloxacin is 500 mg twice daily for 14 days, and the recommended dose of oral doxycycline is 100 mg twice daily for 14 days.[58] Our model allows the user to select the duration of PEP, but assumes that an appropriate dose of antibiotic is administered. Numerous animal PEP studies indicate that symptoms can appear after PEP is discontinued. [59,60,61] Below we outline the efficacy of PEP in preventing the onset of tularemia symptoms and the risk of developing tularemia if the duration of PEP is less than the recommended 14 days.

Efficacy of PEP While on Antibiotics

The efficacy of PEP while on antibiotics was established using animal data, human experimental studies, and human clinical data (described below). The schematic shown below (Figure 19) illustrates the data that influence this modeling parameter.

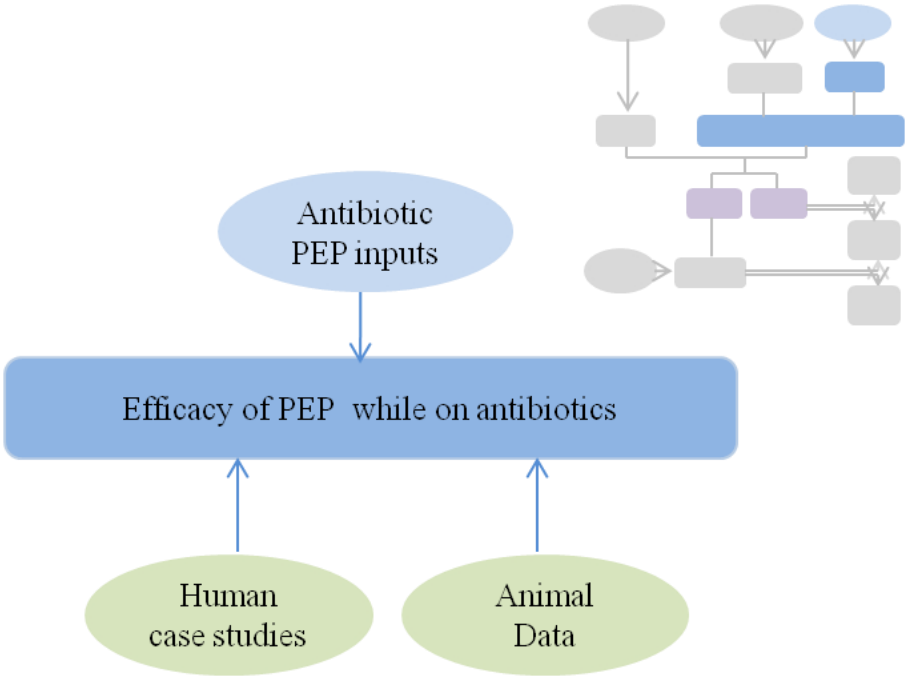

Figure 19. Modeling scheme for the efficacy of PEP while on antibiotics. The light blue oval indicates the user input, the dark blue rectangle indicates the modeling parameter calculations, and green ovals indicate data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

58 Dennis D et al. "Tularemia as a biological weapon: medical and public health management." *JAMA*. **285**(21). 2001.

59 Sawyer W et al. "Antibiotic prophylaxis and therapy of airborne tularemia." *Microbiology and Molecular Biology Reviews.* **30**(3). 1966.

60 Russell P et al. "The efficacy of ciprofloxacin and doxycycline against experimental tularemia." *Journal of Antimicrobial Chemotherapy*. **41**(4). 1998.

61 Peterson J et al. "Protection afforded by fluoroquinolones in animal models of respiratory infections with *Bacillus anthracis, Yersinia pestis,* and *Francisella tularensis.*" *The Open Microbiology Journal.* **4**(34-46). 2010.

Value or Function:

Efficacy of PEP administered before symptoms onset:

$E_{antibiotics}$ = 100% effective at preventing symptom onset while taking the antibiotics

Efficacy of PEP on the day of symptoms onset:

$E_{antibiotics}$ = 0% effective at preventing symptom onset

Where:

$E_{antibiotics}$ = efficacy of antibiotics at preventing symptom onset while taking PEP antibiotics

Individuals for Whom this Parameter Applies:

The "Efficacy of PEP while on Antibiotics" parameter is applied to all individuals that are administered PEP antibiotics. The efficacy of PEP that is applied to each individual is dependent on whether or not PEP was administered before the onset of symptoms.

Rationale:

Both human and animal studies show that disease symptoms do not develop while an appropriate dose of antibiotic PEP is being administered, regardless of whether symptoms develop after PEP is discontinued.[62,63,64] Therefore, we assume that no individuals will develop symptoms for the duration of PEP administration. Appendix 4 describes the studies that support this assertion.

Unfortunately there is very little information in the human and animal literature that describes the efficacy of PEP at preventing symptom onset when administered at various times during the incubation period. The majority of studies were tested at only one time point – usually 24 hours after exposure (see studies in Appendix 4). Despite the lack of variety in time points tested in animal studies, our observations of the efficacy of antibiotic treatment in humans (see the "Treatment with Antibiotics" section and Appendix 5) indicate that antibiotics can be very effective against tularemia, particularly early in the disease. Therefore our model assumes that PEP administered on any day before symptom onset is 100% effective in preventing symptoms, but PEP administered on the same day as symptom onset will not prevent the individual from developing disease.

Efficacy of PEP After Antibiotics are Discontinued

The efficacy of antibiotic PEP in preventing symptom onset after various durations of PEP was established using both human and animal data (described below). Figure 20 is a schematic that illustrates the data influencing this modeling parameter.

[62] Sawyer W et al. "Antibiotic prophylaxis and therapy of airborne tularemia." *Microbiology and Molecular Biology Reviews.* **30**(3). 1966.

[63] Russell P et al. "The efficacy of ciprofloxacin and doxycycline against experimental tularemia." *Journal of Antimicrobial Chemotherapy.* **41**(4). 1998.

[64] Steward J et al. "Treatment of murine pneumonic *Francisella tularensis* infection with gatifloxacin, moxifloxacin or ciprofloxacin." *International Journal of Antimicrobial Agents.* **27**(5). 2006.

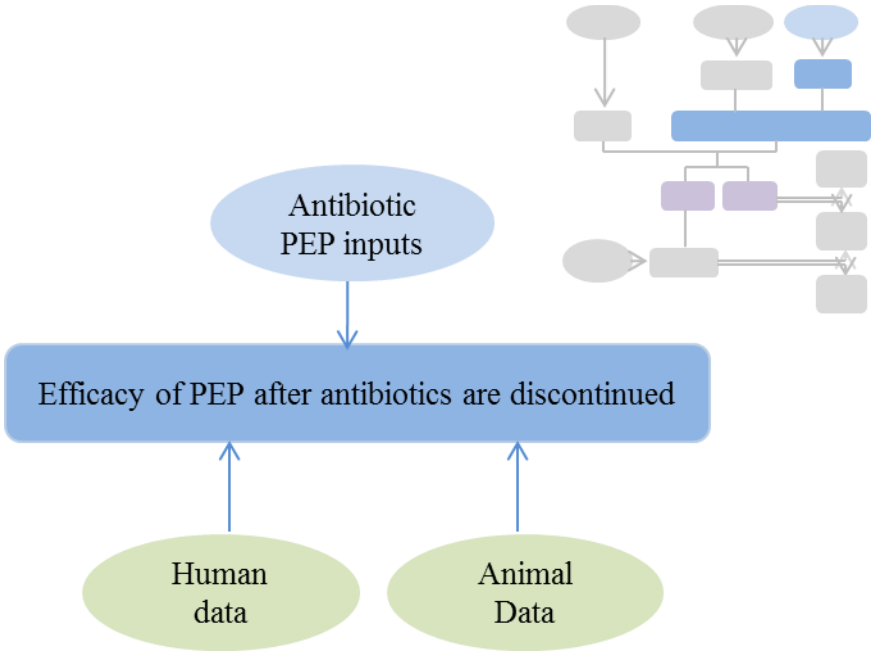

Figure 20. Modeling scheme for the efficacy of PEP after antibiotics are discontinued. The light blue oval indicates user inputs, the dark blue rectangle indicates the modeling parameter calculations, and green ovals indicate data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or Function:

$$E_{discontinued} = {d_{PEP}}^{7.526} \div (8.6664 \times 10^4 + {d_{PEP}}^{7.526})$$

Where:
d_{PEP} = duration of PEP in days
$E_{discontinued}$ = The percentage of individuals who do not develop symptoms following discontinuation of antibiotics that were administered for a duration of d_{pep} days.

Individuals for Whom this Parameter Applies:

In an individual that receives PEP before the onset of symptoms, the "Efficacy of PEP after antibiotics are discontinued" parameter modifies the probability that the individual will develop symptoms after antibiotic PEP is discontinued. The probability of developing symptoms is first calculated based on the individual's exposure dose as if the individual had no MCM (see the "Infectivity" parameter). If the individual would develop symptoms in the absence of PEP, the model then applies the equations above to determine if symptoms still develop given the PEP inputs.

Rationale:

Both human and animal data (detailed in Appendix 4) indicate that PEP is 100% effective at preventing symptoms when given for a duration close to that which is recommended (14 days). One study showed that no humans developed disease when administered 14 days of prophylactic tetracycline, an antibiotic in the same class as doxycycline.[65] Similar results were seen in

[65] Sawyer W et al. "Antibiotic prophylaxis and therapy of airborne tularemia." *Microbiology and Molecular Biology Reviews.* **30**(3). 1966.

monkeys[66] and mice[67,68] administered 10-13 days of levofloxacin, a drug in the same class as ciprofloxacin. However, additional data indicate that animals can develop symptoms if antibiotic PEP is discontinued early in the regimen.[69] We used these human and animal studies to develop a function describing the likelihood that PEP will prevent illness based on the duration of antibiotic administration. Although mice are not an ideal comparison to humans, we used the data from the study described above to inform the shape of the PEP efficacy curve, because no human or monkey data were available for PEP of such short duration. Figure 21 below shows the sigmoidal curve derived from a regression analysis. This shape of the curve reflects the expected result following various durations of antibiotic PEP. In individuals who would otherwise develop symptoms, one would expect there to be a duration sufficient to completely kill bacteria and thus plateau to 100%, and a duration insufficient to kill the bacteria present and thus plateau to 0%. Further details on the studies that were included in our analysis are provided in Appendix 4.

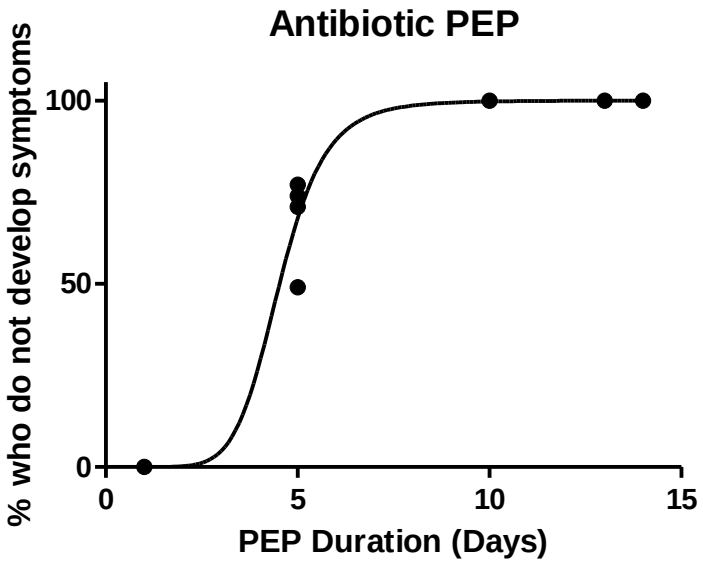

Figure 21. Relationship between the duration of PEP and the percent of individuals who do not develop symptoms (even after PEP are discontinued).

Reduced Severity of Illness in Delayed Onset After PEP

The parameter describing the severity of illness in individuals with delayed onset after PEP was established using human case studies and animal data (described below). The schematic shown below (Figure 22) illustrates the data that influence this modeling parameter.

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66 Nelson M et al. "Bioavailability and efficacy of levofloxacin against *Francisella tularensis* in the common marmoset (*Callithrix jacchus*)." *Antimicrobial Agents and Chemotherapy.* **54**(9). 2010.

67 Although this study tested multiple doses of injected bacteria, there was only a very weak correlation between dose and antibiotic efficacy. Since the data were insufficient to analyze dose, we considered only the average efficacy over all tested doses. If more information becomes available on shortened durations of PEP and delayed onset, it would be worthwhile revisiting the relationship between dose and PEP efficacy.

68 Klimpel G et al. "Levofloxacin rescues mice from lethal intra-nasal infections with virulent *Francisella tularensis* and induces immunity and production of protective antibody." *Vaccine.* **26**(52). 2008.

69 Russell P et al. "The efficacy of ciprofloxacin and doxycycline against experimental tularemia." *Journal of Antimicrobial Chemotherapy.* **41**(4). 1998.

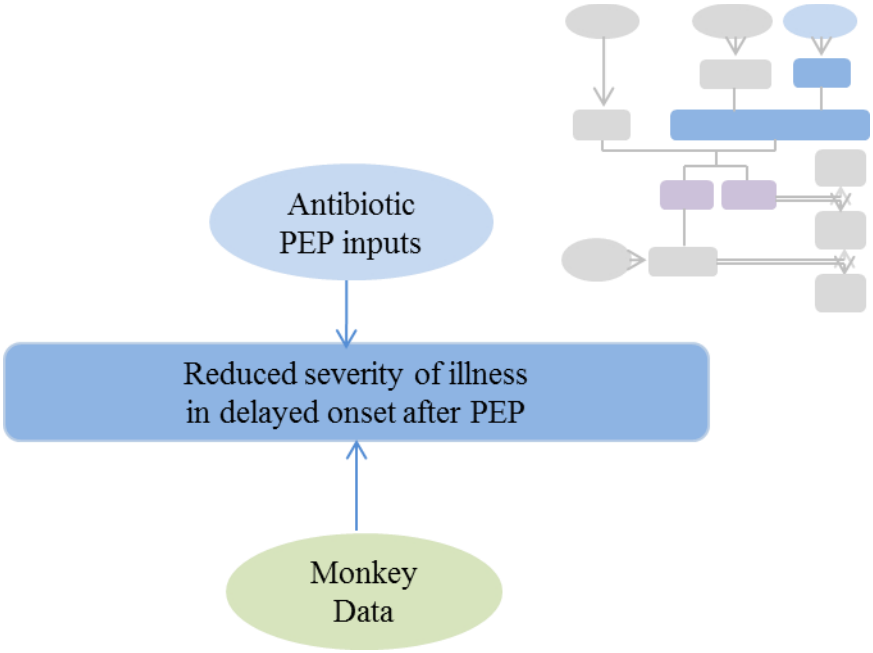

Figure 22. Modeling scheme for the reduced severity of illness in delayed onset after PEP parameter. The light blue oval indicates user inputs, the dark blue rectangle indicates the modeling parameter calculations, and the green oval indicates data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or Function:

Delayed onset mortality rate = 7.5% mortality (10% of initial mortality rate)

Individuals for Whom this Parameter Applies:

The "Reduced severity of illness in delayed onset after PEP" parameter is used in place of the 75% mortality rate described by Curling et al. to calculate the chance of death in individuals that receive PEP but still develop symptoms. This parameter may be modified by other parameters (like the "Efficacy of antibiotics at various treatment times" parameter).

Rationale:

One study of PEP efficacy indicates that monkeys and humans that develop symptoms after discontinuing PEP experience a less severe form of the disease, and that their chance of death is reduced.[70] In this study by Sawyer et al, tetracycline PEP was tested in humans, and eight individuals (all of whom had an inadequate dose or duration of antibiotic) developed symptoms after PEP was discontinued. However, all eight were quickly treated, and therefore the severity of the illness could not be determined. The same study also looked at PEP efficacy in *Macacca mulatta.* Of the ten monkeys that developed symptoms after tetracycline PEP was discontinued, only one died. In comparison, 100% of the control animals died. These monkey data were used to estimate a 90% reduction in the chance of death in untreated individuals who develop tularemia

[70] Sawyer W et al. "Antibiotic prophylaxis and therapy of airborne tularemia." *Microbiology and Molecular Biology Reviews.* **30**(3). 1966.

after PEP is discontinued, giving a mortality rate of 7.5%. We did not find enough information to support other changes to the disease course; therefore, we assume that the duration of the symptomatic period is the same as for the typical disease course.

Timing of Post-PEP Disease Course

The parameter describing the timing of the post-PEP disease course was established using monkey data (described below) and data from Curling et al.[71] The schematic shown below (Figure 23) illustrates the data that influence this modeling parameter.

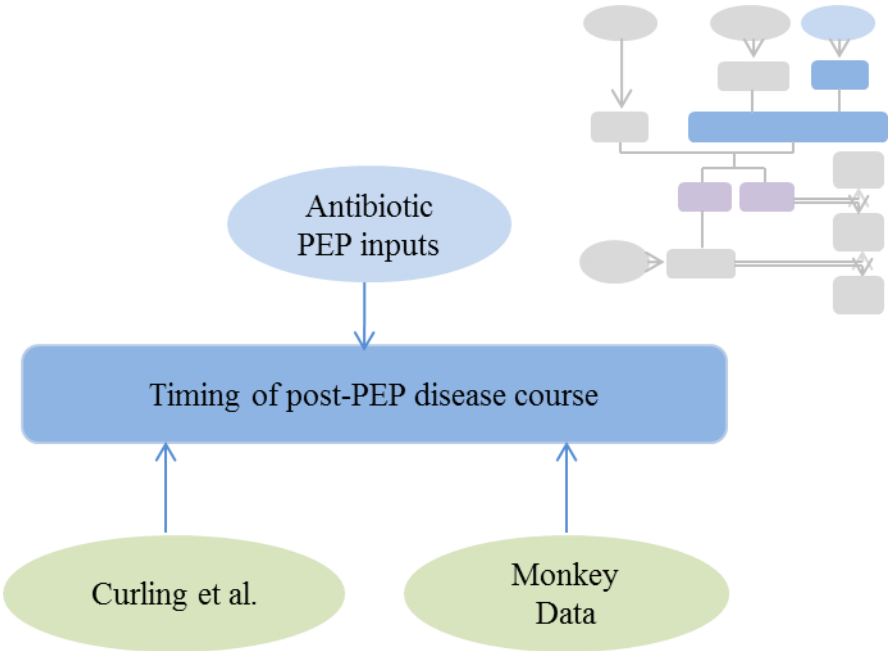

Figure 23. Modeling scheme for timing of the post-PEP disease course. The light blue oval indicates user inputs, the dark blue rectangle indicates the modeling parameter calculations, and the green ovals indicate data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or Function:

Length of the post-PEP incubation period

Equal to the length of to the incubation period experienced following inhalation of five organisms (see the "No MCM Disease Course" section).

Period of fever

Equal to the period of fever experienced following inhalation of five organisms (see the "No MCM Disease Course" section).

Time of symptom onset

Equal to the time when PEP is discontinued plus the post-PEP incubation period.

Individuals for Whom this Parameter Applies:

[71] Curling, C et al. "Parameters for Estimation of Casualties from Exposure to Selected Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia. Volume I: DRAFT 02/07/2011. Tularemia Extract." Institute for Defense Analysis (IDA) Document D-4132, November 2010.

The "Timing of post-PEP disease course after discontinuing PEP" is implemented in individuals who develop symptoms despite receiving PEP.

Rationale:

If the duration of antibiotic PEP is insufficient to prevent the onset of symptoms, patients will develop symptoms after PEP is discontinued due to inadequate clearance of the bacteria. The ID_{50} of tularemia is only 10 organisms,[72] so it is possible that just a few organisms remaining in the body could cause disease. One study of tetracycline PEP in monkeys discussed the timing of delayed onset after PEP was discontinued, saying that "two of six animals developed tularemia within six days of the last dose of drug."[73] According to Curling et al., inhalation of five organisms can cause an incubation period of six days;[74] therefore, we use the disease course distribution for an inhaled dose of five organisms to establish the timing of the disease course after PEP is discontinued.

The time of symptom onset in individuals that develop symptoms despite PEP is calculated by adding the day after exposure that PEP was given, the duration of PEP, and the post-PEP incubation period described above. For example, an individual given PEP one day after exposure for a duration of three days (days one, two and three), and has a post-PEP incubation period of seven days, would develop symptoms on day ten.

Treatment with Antibiotics

Historically, treatment of tularemia with antibiotics has been extremely effective in stemming the organ necrosis that is associated with death.[75] Injected streptomycin is the CDC drug of choice for treatment after the onset of tularemia symptoms. Gentamicin is also recommended by the CDC, although it is not FDA-approved for tularemia treatment. Alternative treatment choices include injected doxycycline, chloramphenicol, and ciprofloxacin.[76] Bacteriostatic agents, like doxycycline and chloramphenicol, require a longer duration of treatment than bacteriocidal agents, and insufficient duration of treatment with a bacteriostatic agent can result in relapse.[77] The data from clinical tularemia cases indicate that treatment with bacteriocidal antibiotics can also result in relapse, although at a very low rate. For the purpose of our model, we assume that individuals who fall ill will be treated with injected streptomycin or gentamicin and that antibiotic treatment will be continued for the full recommended regimen of ten days. We also assume that those who relapse after treatment will be treated again and recover. Below we describe the efficacy of antibiotics, the rate of relapse after the recommended treatment regimen, the severity of relapse, and the timing of relapse.

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72 Curling, C et al. "Parameters for Estimation of Casualties from Exposure to Selected Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia. Volume I: DRAFT 02/07/2011. Tularemia Extract." Institute for Defense Analysis (IDA) Document D-4132, November 2010.

73 Sawyer W et al. "Antibiotic prophylaxis and therapy of airborne tularemia." *Microbiology and Molecular Biology Reviews.* **30**(3). 1966.

74 Curling, C et al. "Parameters for Estimation of Casualties from Exposure to Selected Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia. Volume I: DRAFT 02/07/2011. Tularemia Extract." Institute for Defense Analysis (IDA) Document D-4132, November 2010.

75 Twenhafel NA, Alves DA and Purcell BK. "Pathology of Inhalational *Francisella tularensis* SCHU S4 Infection in African Green Monkeys *(Chlorocebus aethiops)*." *Veterinary Pathology Online.* **46**(4). 2009.

76 Dennis DT et al. "Tularemia as a biological weapon: medical and public health management." *JAMA.* **287**(4). 2002.

77 Enderlin G et al. "Streptomycin and alternative agents for the treatment of tularemia: review of the literature." *Clinical Infectious Diseases.* **19**(1). 1994.

Efficacy of Antibiotics at Various Treatment Times

The parameter describing the efficacy of treatment with antibiotics at various times was established using human case studies, human experimental studies, and animal data (described below). The schematic shown below (Figure 24) illustrates the data that influence this modeling parameter.

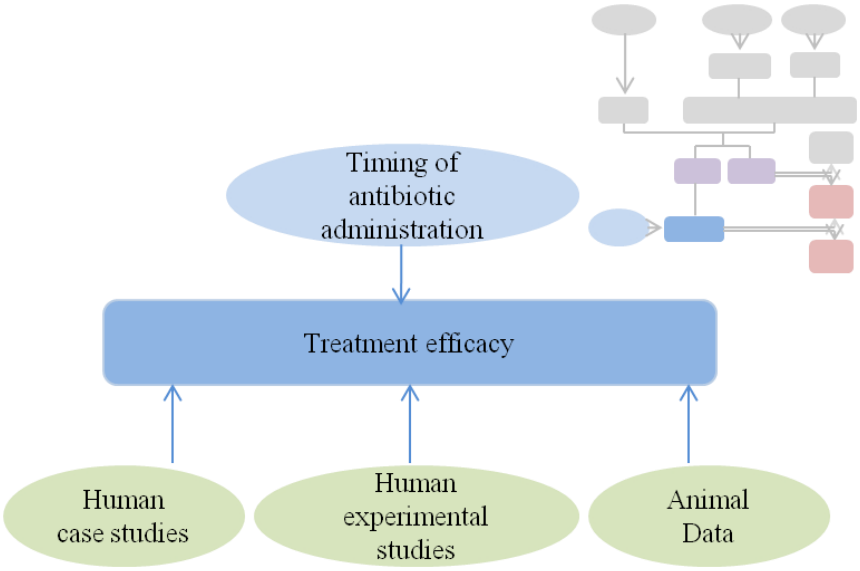

Figure 24. Modeling scheme for efficacy of antibiotics at various treatment times. The light blue oval indicates the user input, the dark blue rectangle indicates the modeling parameter calculations, and the green ovals indicate data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or Function:

Table 2. Efficacy of Antibiotics at Various Treatment Times

Treatment Time	Efficacy
>1 day before death	100%
1 day before death	50%
0 day before death	0%

Individuals for Whom this Parameter Applies:

In individuals treated with antibiotics, the "Efficacy of antibiotics at various treatment times" parameter modifies the chance of death in an individual by the values described above. The model first calculates the chance and timing of death if the individual were untreated, and then reduces the chance of death by the values given above based on the timing of treatment in comparison with the untreated time of death. If an individual's untreated chance of death was 0%, then treatment will not affect the individuals' chance of dying.

Rationale:

The parameter describing efficacy of tularemia treatment was developed using data from both animals and humans. The animal data include three studies which examine the efficacy of antibiotic treatment at various time points after exposure (two studies of levofloxacin-injected

mice[78,79] and one study of streptomycin-injected guinea pigs[80]). All three studies show that antibiotics are very effective when administered soon after exposure, but that the efficacy of treatment wanes when first administered in the days before death.

In the two mouse studies described above, mice treated more than one day before the mean time to death (MTTD) of the control animals had 80-100% survival, while those treated approximately one day before the control MTTD had 0-80% survival rate, and those treated less than one day before the MTTD had a 0% survival rate. The data from these two mouse studies indicate that although treatment can be very effective early in the symptomatic period, treatment becomes progressively less effective when initiated close to the time of death. The data from the guinea pig study show a similar trend, but have a lower maximum survival rate. Details of the animal studies used in our analysis are described in Appendix 5.

Data from human experimental studies corroborate our analysis of the data from animal studies. Human experiments of inhaled tularemia show that antibiotic treatment early after the onset of disease is extremely effective (see Tables A-9 and A-10 of Appendix 5 for details). Nineteen patients in these studies were treated very early in the symptomatic period (either the day of symptom onset or the day after symptom onset). All 19 recovered completely and without complication. These human cases support our assertion that treatment early in the symptomatic period is 100% effective.

In addition to the experimental human studies, we included clinical case studies in our analysis (Appendix 5); however, only patients that were treated with a relevant antibiotic (streptomycin or gentamicin), and whose disease likely resulted from an exposure to Type A *F. tularensis* were included (see Appendix 5). Although inhalation of an aerosol is the most relevant exposure route in a military scenario, we considered clinical data from all routes of exposure for two reasons. First, clinical reports that describe an illness clearly caused by inhalation are extremely scarce; many clinical cases do not include information about exposure at all. Second, including data on treatment efficacy from all exposure routes in our analysis did not change our conclusions. Therefore, we included data from human cases caused by all exposure routes in order to encompass as much of the clinical picture of tularemia as possible.

Of the 413 clinical patients included in our analysis, 410 survived after treatment (see Table A-9 and A-10 in Appendix 5). Some of these patients were treated as early as one day after symptom onset while others were not treated until more than a month after symptom onset. The data from these human clinical case reports further support our assessment of the high treatment efficacy early in the symptomatic period. All three of the patients who died were first treated with effective antibiotics within 24 hours of their death.[81,82,83] We found examples of two other fatal cases, in which antibiotics were first administered on the ninth and thirty-first days after symptom

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78 Peterson JW et al. "Protection Afforded by Fluoroquinolones in Animal Models of Respiratory Infections with *Bacillus anthracis*, *Yersinia pestis*, and *Francisella tularensis*." *The Open Microbiology Journal.* **4**. 2010.

79 Klimpel GR et al. "Levofloxacin rescues mice from lethal intra-nasal infection with virulent *Francisella tularensis* and induces immunity and production of protective antibody." *Vaccine.* **26**(52). 2008.

80 Libich J. "Effect of the administration of streptomycin in the incubation and manifest phase on the course of inhalation tularemia in guinea pigs." *Folia Micobiologica.* **7**:320-5. 1962.

81 This death was associated with a Jarish-Herxheimer-like reaction. Evans M et al. "Tularemia: a 30-year experience with 88 cases." *Medicine.* **64**(4). 1985.

82 Foshay L. "Treatment of tularemia with streptomycin." *The American Journal of Medicine.* **2**(5). 1947.

83 Shapiro DS and Schwartz DR. "Exposure of laboratory workers to *Francisella tularensis* despite a bioterrorism procedure." *Journal of Clinical Microbiology.* **40**(6). 2008.

onset,[84] but these cases could not be included in our analysis because the report did not include data on the duration of treatment before death. Because death in tularemia is associated with overwhelming organ burden and organ necrosis,[85] and all of the individuals for whom there is data died within 24 hours of receiving antibiotics, we conclude that antibiotics administered on the day of death are unable to rescue the patient from tissue damage and are thus 0% effective. These human case studies are supported by the animal data, which also indicate that treatment close to the time of death is ineffective.

Although the human experimental and clinical studies indicate that antibiotic treatment is generally very effective (Appendix 5), the animal data suggest a decrease in efficacy over several days immediately preceding death (Appendix 5). Assuming the minimum ten days of treatment, our model estimates that antibiotics are 100% effective if administered more than one day before death, 50% effective if administered one day before death, and 0% effective if administered within 24 hours of death.

Duration of Fever in A Treated Individual who Recovers

Studies on human volunteers infected with *F. tularensis* have shown that fever is closely correlated to decreased work performance;[86] therefore, we analyzed how many days of fever are experienced by individuals who recover from the disease. Human data (described below) suggest that the longer the delay between symptom onset and the start of antibiotic treatment, the longer it takes for fever to resolve. The schematic shown below (Figure 25) illustrates the data that were used to establish the parameter describing the length of the febrile period.

[84] Rosenthal J. "Tularemia treated with streptomycin. Analysis of fifty-four cases." *The New Orleans Medical and Surgical Journal."* **103**(11). 1951.

[85] Twenhafel NA, Alves DA and Purcell BK. "Pathology of Inhalational *Francisella tularensis* SCHU-S4 Infection in African Green Monkeys *(Chlorocebus aethiops)*." *Veterinary Pathology Online.* **46**(4). 2009.

[86] Anno et al. Consequence Analytic Tools for NBC Operations, Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever. Defense Special Weapons Agency. 1998.

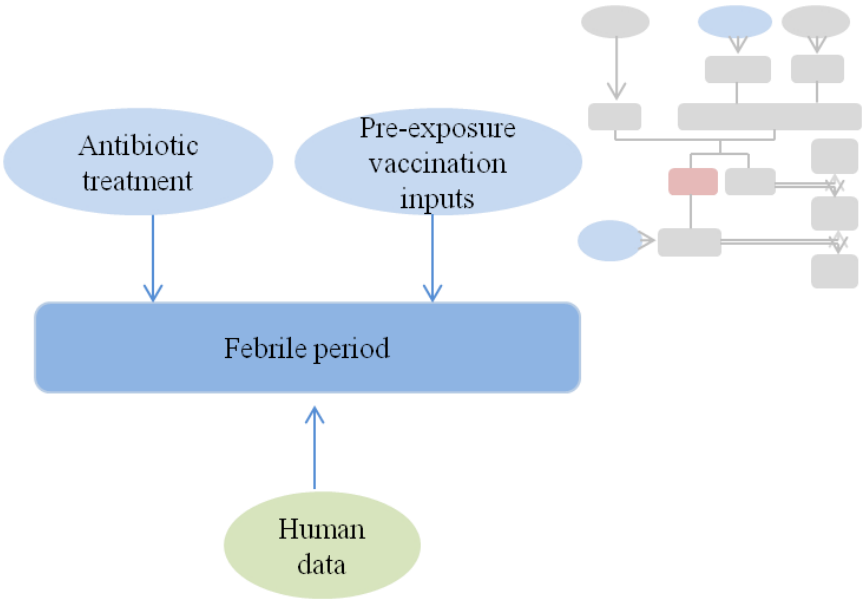

Figure 25. Modeling scheme for febrile period. Light blue ovals indicate user inputs, the dark blue rectangle indicates the modeling parameter calculations, and the green oval indicates data used to establish these parameters. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or function:

For all individuals treated with antibiotics:

$$Mean\ total\ period\ of\ fever = df_{before} + df_{after}$$
$$df_{after} = 1.027 + 0.3177 * df_{before}$$
$$SD\ for\ df_{after} = 0.3274 + 0.2816 * df_{before}$$

Where:
df_{before} is the days of fever before treatment is first administered
df_{after} is the additional days of fever after the start of treatment

Individuals for Whom this Parameter Applies:

While the "duration of fever" parameter described earlier in this report calculates the period of fever in untreated individuals, it is replaced by this parameter in all treated survivors. If treatment is only made available after fever has subsided, or if the period of fever in an untreated survivor is less than the period calculated above, then no change is made to the untreated period of fever.

Rationale:

Data from experimental human respiratory infections with *F. tularensis* and case studies of pulmonary tularemia suggest that the duration of fever following administration of effective antibiotics is dependent on how quickly antibiotics are administered.[87,88,89,90,91] Fever typically

[87] Feign RD and Dangerfield HG. "Whole blood amino acid changes following respiratory-acquired *Pasteurella tularensis* infection in man." *J Infect Dis*. **117**(4). 1967.
[88] Sawyer WD et al. "Antibiotic Prophylaxis and Therapy of Airborne Tularemia." *Bacteriological Reviews*. **30**(3). 1966.
[89] Parker RT et al. "Use of chloramphenicol (chloromycetin) in experimental and human tularemia." *JAMA*. **143**(1). 1950.
[90] Atwell RJ and Smith DT. "Primary Tularemia Pneumonia Treated with Streptomycin." *Southern Medical Journal*. **30**(11). 1946.

resolves rapidly in individuals who receive treatment soon after its onset; however, if treatment is delayed, the period of time required for a patient to become afebrile is greater. Figure 26 below demonstrates the relationship between the time of antibiotic administration and the length of the febrile period after antibiotic administration. See Appendix 6, Table A-12 for the data that were used to create this figure. Our model uses the equation of the solid line in Figure 26 to describe the mean period of fever after administration of antibiotics; the standard deviation is represented by the dotted lines. Since we did not find any information on the duration of fever in treated individuals with mild disease, we assume that the calculation defined in this parameter is applicable for all survivors regardless of the severity of the disease.

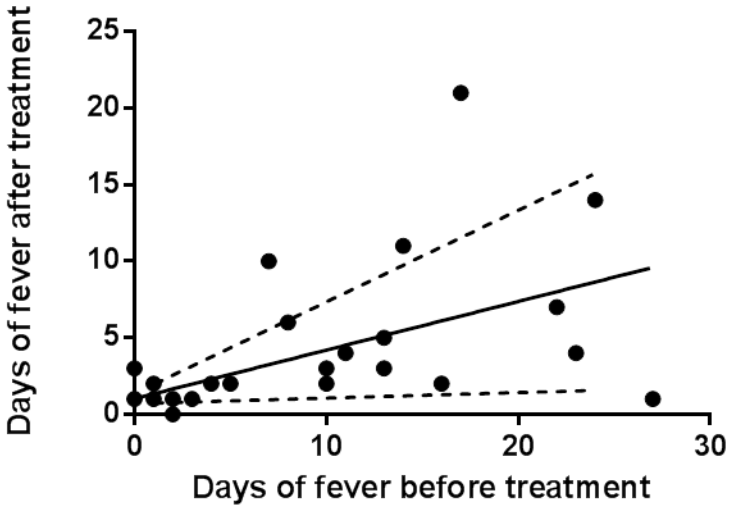

Figure 26. Relationship between timing of antibiotic treatment and period of fever. The solid line indicates the mean number of days of fever after treatment, given by the equation $df_{after} = 1.027 + 0.3177 * df_{before}$ where df_{before} is the days of fever before treatment and df_{after} is the additional days of fever after treatment. The dotted lines are one standard deviation away from the mean. The standard deviation is given by the equation: $SD = 0.3274 + 0.2816 * df_{before}$.

Rate of Relapse After Completing Treatment Regimen

The parameter describing the rate of relapse after completing an antibiotic treatment regimen was established using data from human clinical cases (described below). The schematic shown below (Figure 27) illustrates the data that influence this modeling parameter.

[91] Berson RC. "Streptomycin in the Treatment of Tularemia." *The American Journal of the Medical Sciences*. **215**(3). 1948.

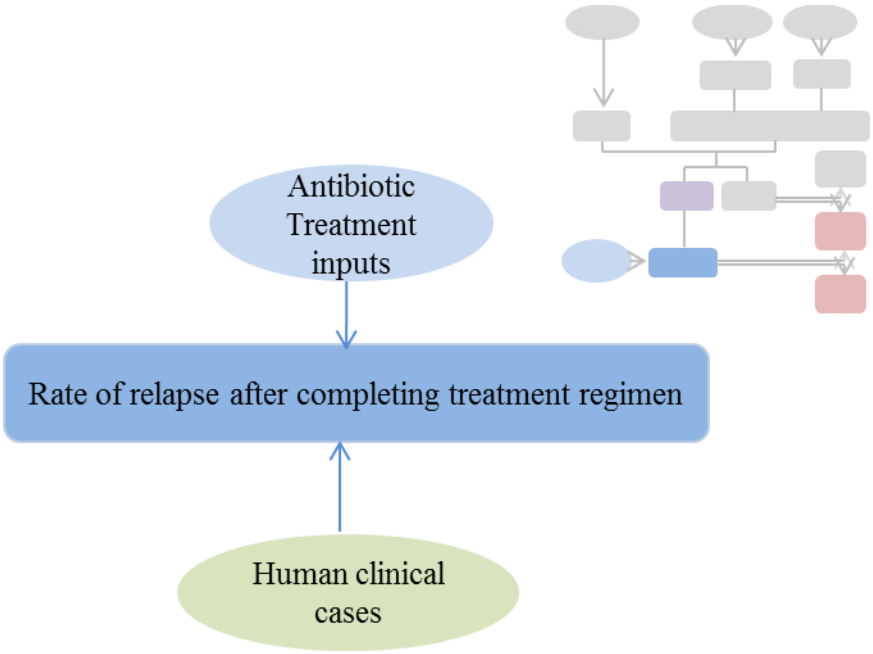

Figure 27. Modeling scheme for rate of relapse after completing the treatment regimen. The light blue oval indicates the user input, the dark blue rectangle indicates the modeling parameter calculations, and the green oval indicates data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or Function:

Rate of relapse after completing treatment = 2%

Individuals for Whom this Parameter Applies:

This parameter determines the probability that symptomatic individuals who recover following treatment will experience relapse after the treatment is discontinued.

Rationale:

Of the 432 human cases included in our analysis of antibiotic treatment (including 19 experimental and 413 naturally exposed patients), 12 (2.8%) suffered a relapse after treatment was discontinued (Table A-11, Appendix 5). If only those patients of military age (18-62 years old) are analyzed, eight of 354 patients relapsed (2.26%). Many of these patients did not receive the full ten days of antibiotics recommended for treatment, but analyzing only patients treated with a full course results in an even greater likelihood of relapse (3.13% of military age patients). However, there may be a bias in the published literature for reporting more severe cases, which would account for the slight increase in relapse after longer treatment durations. Therefore, our model assumes a more conservative estimate of a 2% chance of relapse. Cases of relapse are described in detail in Appendix 5.

Timing of Relapse Onset

The parameter describing the timing of relapse onset after antibiotic treatment is discontinued was determined using data from human clinical cases (described below). The schematic shown below (Figure 28) illustrates the data that influence this modeling parameter.

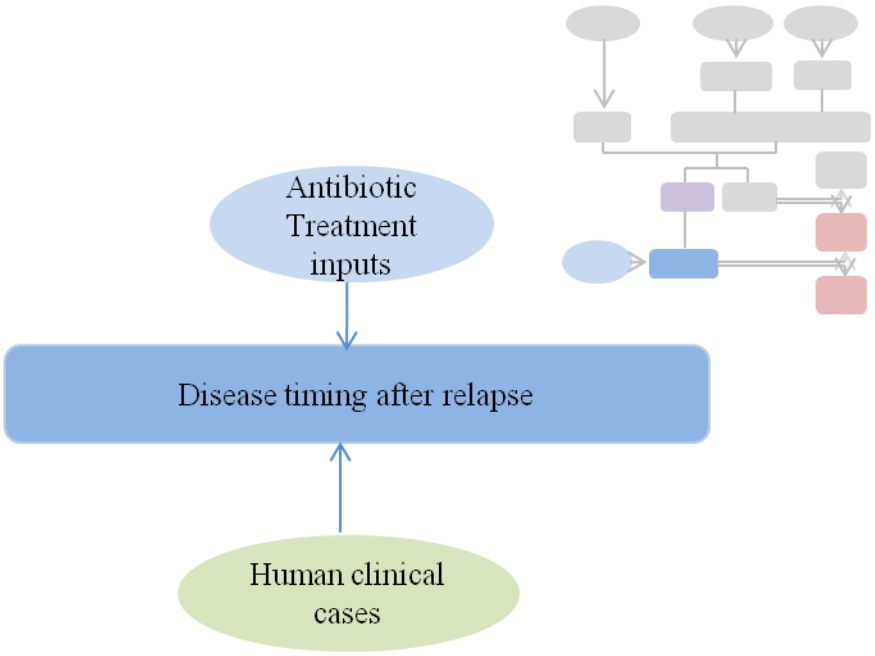

Figure 28. Modeling scheme for disease timing after relapse. The light blue oval indicates the user input, the dark blue rectangle indicates the modeling parameter calculations, and the green oval indicates data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or Function:

The length of time between antibiotics being discontinued and relapse is a lognormal distribution where:

σ = 1.71681057, the mean of the natural logs of the observed values
μ = 0.665761329, the standard deviation of the natural logs of the observed values

Individuals for Whom this Parameter Applies:

For treated individuals who relapse after antibiotics are discontinued, this parameter determines the duration of time from when antibiotics are discontinued until symptoms will begin again.

Rationale:

Of the twelve patients who relapsed after antibiotic treatment, data describing the length of time between when antibiotics were discontinued and when relapse occurred was available for ten. Of these patients, the average time until relapse was 6.8 days, with a range of 2-18 days. Based on this data (which is provided in Table A-11 in Appendix 5) our model uses a lognormal distribution to describe the time until relapse after discontinuing antibiotic treatment. Our model assumes that those who relapse after antibiotic treatment will be further treated with antibiotics for the recommended duration of 10 days and will recover after the second treatment.

MCM Adverse Effects and Recovery

F. tularensis is not always deadly even in untreated individuals; however, individuals that develop disease and some who take prophylactic antibiotics to prevent the onset of symptoms will be unable to work for one or more days due to adverse effects from the antibiotics.[92] Therefore, in addition to calculating an

[92] Side effects from vaccination are assumed to occur before exposure, and therefore are not considered in this model.

individual's chance of dying, our model calculates work lost as a result of infection and/or antibiotic use. We define "work performance" as the intellectual and physical ability to perform the tasks required of a warfighter,[93] and we define the inability to perform such tasks as "loss of work." Loss of work due to tularemia can result from adverse effects of MCM administered, or from illness and recovery. The sections below describe the loss of work from PEP antibiotics, and the days of work lost due to illness in an individual who recovers. The work lost parameters are intended to provide a useful output for military planners to determine the period of time warfighters would be unable to perform their duties.

Although Curling et al.[94] describe a 12-week recovery period (called Stage 3) in their model of disease, the recovery of those treated with antibiotics differs from that seen in untreated survivors. To accommodate the differences in treated and untreated individuals, we developed an alternate method of determining the recovery period, based on evidence from case studies (see "Days of work lost due to illness in an individual who recovers"). Thus the work lost due to illness parameter includes the entire period of fever (Stage 1 and Stage 2) as well as an additional period of recovery.

Loss of Work from PEP Antibiotics

Ciprofloxacin and doxycycline are indicated for use as post-exposure prophylaxis both for *F. tularensis* and *Bacillus anthracis*, the causative agent of anthrax. Following the 2001 Amerithrax attacks these antibiotics were administered to individuals potentially exposed to anthrax. Since *F. tularensis* and *B. anthracis* use the same PEP antibiotics, the dataset from the Amerithrax attack, which provides information about antibiotic-related adverse effects in otherwise healthy individuals, was used to establish our parameter describing the loss of work from PEP antibiotics. The schematic shown below (Figure 29) illustrates the data that were used to establish this parameter and how the parameter fits into the larger modeling scheme shown in Figure 1.

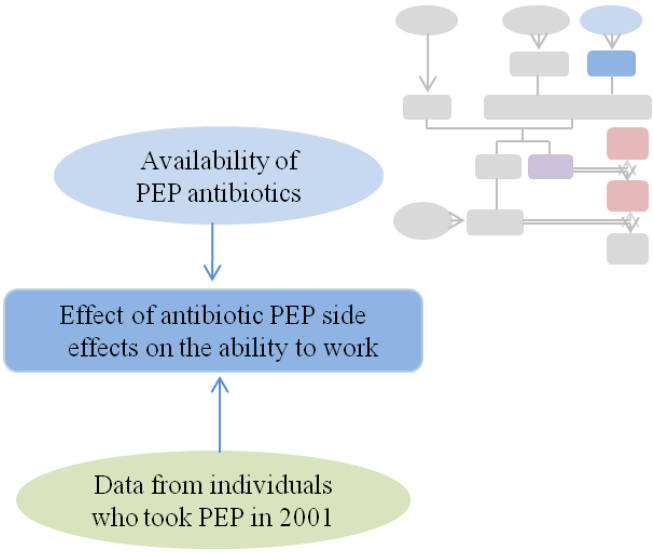

Figure 29. Modeling scheme for loss of work following antibiotic PEP. The light blue oval indicates user inputs, the dark blue rectangle indicates the modeling parameter calculations, and the green oval indicates data used to establish these parameters. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

[93] Alluisi, Thurmond and Coates. *Behavioral Effects of Infectious Diseases: Respiratory Pasteurella Tularensis, Perceptual and Motor Skills*, Vol. 32. 1971.

[94] Curling, C et al. "Parameters for Estimation of Casualties from Exposure to Selected Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia. Volume I: DRAFT 02/07/2011. Tularemia Extract." Institute for Defense Analysis (IDA) Document D-4132, November 2010.

Value or Function:

Table 3. Loss of Work from PEP	
1 day loss of work	5% of individuals taking PEP
2 day loss of work	5% of individuals taking PEP
3 day loss of work	3% of individuals taking PEP
7 day loss of work	1% of individuals taking PEP

Individuals for Whom this Parameter Applies:

For individuals who receive PEP but do not develop symptoms, this parameter determines the number of days of work lost. Work lost due to PEP is not calculated in individuals that develop symptoms, since we assume that work lost due to illness is generally much greater than work lost due to PEP (see the "Days of work lost due to illness in an individual who recovers" parameter below).

Rationale:

Ciprofloxacin and doxycycline antibiotics are indicated for post-exposure prophylaxis following inhalation of *F. tularensis*.[95] These two drugs, taken as PEP following the 2001 Amerithrax mailings, produced a wide range of adverse side effects, including gastrointestinal symptoms, fainting, dizziness, light-headedness, seizures, and rash, hives, or itchy skin. Rates of these adverse effects did not vary substantially between the two antibiotics.[96] Approximately 16% of those receiving antibiotics as PEP reported seeking medical care due to adverse effects of the drugs, and 14% reported missing at least one day of work.[97] Only 3% of individuals taking prophylactic ciprofloxacin discontinued it due to adverse events.[98]

In the absence of details about the average number of days of work missed in the Amerithrax mailing cases, we based our parameter on the following assumptions. Of the 3% of individuals that experienced symptoms severe enough to warrant discontinuing the antibiotic, two-thirds (2%) will miss three days of work, at which point they will change to a different antibiotic. The other one-third (1%) will miss a full week of work due to more serious aeffects. Of the other 11% who miss work, we assume 5% miss one day, 5% miss two days, and 1% miss three days, which brings the total that miss three days to 3%.

Days of Work Lost Due To Illness in an Individual Who Recovers

Human data (described below) suggest that the longer an individual with tularemia remains ill and febrile, the longer it takes for them to recover. The schematic shown below (Figure 30) illustrates the data that were used to establish the number of days of work lost in an individual who recovers from tularemia on their own or following treatment. We assume that work lost due to the adverse side effects of treatment

[95] CDC. "Tularemia: Abstract 'Consensus Statement' by Dennis et al." July 1 2005. http://www.bt.cdc.gov/agent/tularemia/tularemia-biological-weapon-abstract.asp#4. Accessed on May 19, 2011. Abstracted from: Dennis D et al. "Tularemia as a biological weapon: medical and public health management." *JAMA*. **285**(21). 2001.

[96] Shepard CW et al. "Antimicrobial Postexposure Prophylaxis for Anthrax: Adverse Events and Adherence." *Emerging Infectious Diseases.* **8**(10). 2002.

[97] Shepard CW et al. "Antimicrobial Postexposure Prophylaxis for Anthrax: Adverse Events and Adherence." *Emerging Infectious Diseases.* **8**(10). 2002.

[98] "Ciprofloxacin Side Effects." http://www.drugs.com/sfx/ciprofloxacin-side-effects.html#ixzz10O2Ht2fj Accessed on Oct 10, 2011.

antibiotics is negligible in comparison to work lost due to illness; therefore the adverse effects of treatment are not included in this parameter.

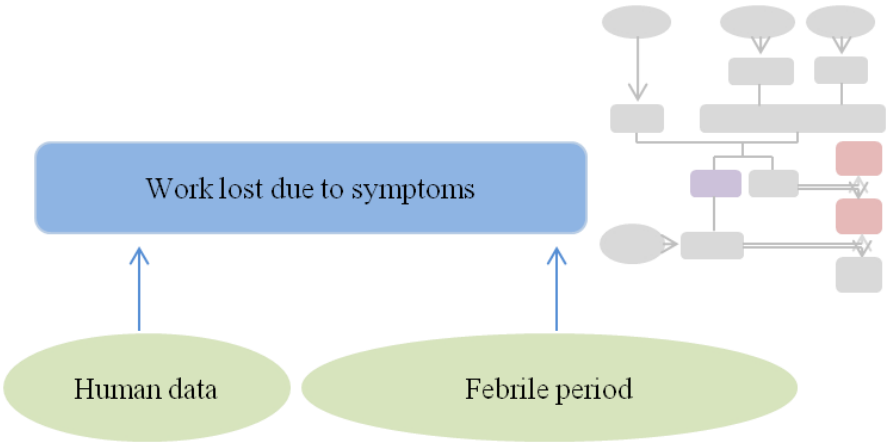

Figure 30. Modeling scheme for loss of work due to symptoms. The dark blue rectangle indicates the modeling parameter calculations and green ovals indicate data used to establish this parameter. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or function:

Days of work lost due to symptoms is a lognormal distribution*:

Mean: 217% of the total number of days of fever

Standard Deviation: 45% of the total number of days of fever

Where the total number of days of fever is defined in the previously described "Days of fever in an individual who recovers" parameter

*Regardless of model calculations, the model output is never less than the minimum days of work lost given below.

Minimum days of work lost due to symptoms in antibiotic treated individuals with typical illness:

Equal to the number of days of fever before treatment is administered (df_{before}) + 14 days

Minimum days of work lost due to symptoms in untreated individuals with typical illness:

Equal to the total number of days of fever

Minimum days of work lost due to symptoms in treated and untreated individuals with mild illness:

Equal to the total number of days of fever

Work lost in individuals who relapse:

Individuals who relapse experience an additional 14 days of work lost

Individuals for Whom this Parameter Applies:

This parameter is applied to all symptomatic individuals who live. The minimum number of days of work lost output by the model is dependent on whether that individual experiences mild or typical illness and whether or not the individual relapses.

Rationale:

Studies on human volunteers infected with *F. tularensis* have been carried out to establish how their work performance is reduced due to tularemia.[99,100] Work performance is defined as the intellectual and physical ability to perform tasks,[101] and a reduction in work performance is described as "performance decrement," or work lost. [102] The Human Performance Resource Center has suggested that 60% effectiveness is the lowest level of performance acceptable for a warfighter.[103] According to Anno et al.[104] this 60% threshold is reached when an individual's fever is around 103°F (see Appendix 6 for more information). Curling et al indicate that high fever occurs at the onset of Stage 1 of the symptomatic period and continues for the duration of Stage 2.[105] This assertion is supported by case studies (Table A-12 in Appendix 6) that indicate that individuals with tularemia typically have a fever that exceeds 103°F.[106] An algorithm for the period of degraded performance described by Anno et al. predicts that individuals will be back to 100% capacity as soon as the fever resolves;[107] however, this algorithm was established using data from individuals treated very shortly after the appearance of symptoms, and even the authors suggest it is likely to be overly optimistic. The case studies included in our analysis (detailed in Table A-13 in Appendix 6) suggest that it takes individuals 117% (standard deviation 45%) of the febrile period to recover.[108,109,110] Our model calculates the period of work lost by multiplying the duration of fever by 217% (SD 45%); therefore the period of work lost includes Stage 1, Stage 2, and an additional recovery period. For example individuals who experienced a fever for 16 days will be unable to work for a total of 35 days (16 fever days plus 19 recovery days).

For treated individuals with typical illness, our model assumes a minimum of 14 days of work lost after the initiation of antibiotics before the individual can return to work. Since antibiotics are administered intravenously, individuals will not be able to work during the ten day period in which they are receiving antibiotics. We also assume that individuals will not return to work immediately upon being released from the hospital; therefore we assume a minimum of two weeks from antibiotic administration until return to work. Using this same rationale, we also assume those who relapse will require two additional weeks to recover before they are able to return to work. Both of these assumptions can be adjusted up or down using the model's advanced users tab.

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99 Anno et al. Consequence Analytic Tools for NBC Operations, Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever. Defense Special Weapons Agency. 1998.

100 Alluisi, Thurmond and Coates. *Behavioral Effects of Infectious Diseases: Respiratory Pasteurella Tularensis, Perceptual and Motor Skills*, Vol. 32. 1971.

101 Alluisi, Thurmond and Coates. *Behavioral Effects of Infectious Diseases: Respiratory Pasteurella Tularensis, Perceptual and Motor Skills*, Vol. 32. 1971.

102 Anno et al. Consequence Analytic Tools for NBC Operations, Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever. Defense Special Weapons Agency. 1998.

103 Human Performance Resource Center (HPRC). "How much sleep does a Warfighter need?" http://humanperformanceresourcecenter.org/mind-tactics/hprc-articles/how-much-sleep-does-a-warfighter-need. Accessed on Sept 26, 2011. HPRC is a Department of Defense initiative under the Force Health Protection and Readiness Program.

104 Anno et al. Consequence Analytic Tools for NBC Operations, Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever. Defense Special Weapons Agency. 1998.

105 Curling, C et al. "Parameters for Estimation of Casualties from Exposure to Selected Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia. Volume I: DRAFT 02/07/2011. Tularemia Extract." Institute for Defense Analysis (IDA) Document D-4132, November 2010.

106 Table 3-1 from: Anno et al. Consequence Analytic Tools for NBC Operations, Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever. Defense Special Weapons Agency. 1998.

107 Anno et al. Consequence Analytic Tools for NBC Operations, Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever. Defense Special Weapons Agency. 1998.

108 Berson RC. "Streptomycin in the Treatment of Tularemia." *The American Journal of the Medical Sciences*. **215**(3). 1948.

109 Rosenthal. "Tularemia Treatment with Streptomycin." *New Orleans Med Surg J*. **103**(11). 1951.

110 Foshay L. "Treatment of Tularemia with Streptomycin." *The American Journal of Medicine*. **2**(5). 1947.

For individuals who have a reduced severity of illness due to vaccination (Mild Type I and Mild Type II illness), our model assumes a minimum duration of work lost equal to the period of fever. Since the mortality rate with mild illness is 0%, we assume that individuals with mild illness can be treated as outpatients and have the potential to return to work as soon as fever resolves. For untreated survivors who receive no MCM, our model also assumes a minimum duration of work lost equal to the period of fever.

Number of Survivors With Chronic Tularemia

Case study data (described below) suggest that a small percentage of individuals who recover from tularemia experience a chronic form of the disease. The schematic shown below (Figure 31) illustrates the data that were used to establish the number of survivors who experience chronic tularemia.

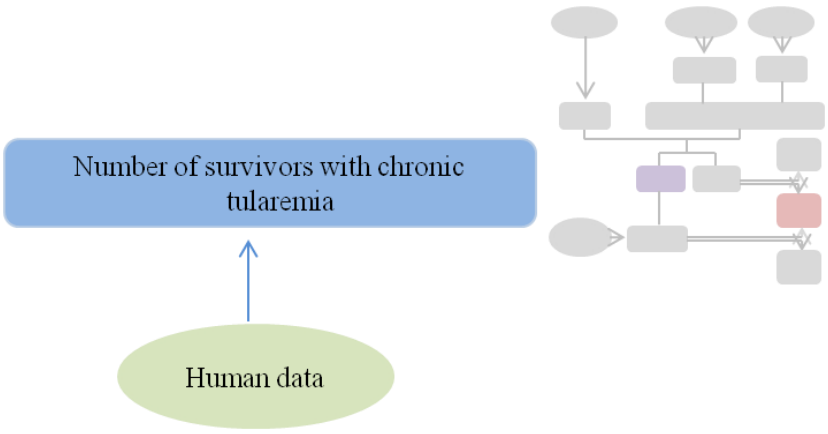

Figure 31. Modeling scheme for the number of survivors with chronic tularemia. The blue rectangle indicates the modeling parameter calculations and the green oval indicates data used to establish these parameters. The inset image shows the parts of the larger Figure 1 modeling scheme that are affected by this parameter.

Value or function:

Percent of treated or untreated survivors who will experience chronic tularemia = 5%

Individuals for Whom this Parameter Applies:

This parameter is applied to all symptomatic individuals who live.

Rationale:

Although tularemia is typically thought of as an acute disease, a persistent mild malaise described as chronic tularemia is occasionally mentioned in the tularemia literature; however, details about the chronic manifestation of the disease are scarce. A report prepared by the Center for Research Information, Inc. for the National Academies suggests that this may be because only one carefully documented study of chronic tularemia exists in the literature.[111] Though the cases are not detailed, Overholt et al. reported that two of the forty-two cases of laboratory-acquired tularemia analyzed in their study experienced mild, persistent symptoms after resolution of acute symptoms.[112] Although the Overholt data set is small and includes patients that developed disease

[111] The Center for Research Information, Inc. "Health Effects of Project Shad Biological Agent: Pasteurella [Francisella] Tularensis [Tularemia]." Contract No. IOM-2794-04-001 Prepared for the National Academies.

[112] Overholt EL et al. "An Analysis of Forty-Two Cases of Laboratory-Acquired Tularemia." *Am J Med*. **30**. 1961.

despite vaccination, we used this information to establish our chronic tularemia modeling parameter due to the lack of other data on this topic. Thus, our model assumes that 5% of individuals that develop symptoms and recover (with or without the help of antibiotics) will develop chronic tularemia. Given the mild nature of chronic tularemia, it is unlikely to cause warfighter performance to drop below the 60% threshold that would result in loss of work (as described in "Days of work lost due to illness in an individual who recovers"). Therefore, our model does not report any loss of work as a result of chronic tularemia.

Calculations and Computational Framework

The sections below describe the calculations and computational framework of our Excel-based MCM model for botulinum neurotoxin. The influence of user inputs (including dose, vaccination inputs, and treatment inputs) on modeling calculations is described. The framework for the stochastic MCM model is then outlined as a step-by-step process, including a description of the incorporation of random number generators.

How User Inputs Influence Model Calculations

The tularemia model described in this document displays both intermediate and final outcomes for each individual based on the underlying parametric values described in the previous section. Intermediate outcomes include whether or not symptoms develop, the timing of symptom onset, the duration of fever, and whether relapse occurs. Final outcomes include survival or death, time of death, work lost due to illness, work lost due to MCM, and the presence or absence of chronic tularemia. These intermediate and final outcomes listed below in Table 4 are displayed on the "Outputs" tab of the Excel model for each individual.

Table 4. Modeling Outputs for Each Individual (Outputs Tab)

Output	Display Options
Symptoms	Not Sick/Sick
Death	Not Sick/Live
Day of Symptom Onset	Days after exposure/No Symptoms
Period of Fever (days)	Length of period of fever (days)/NA
Day of death	Days after exposure/NA
Work lost due to PEP Side Effects	Yes/No/Dead
Days of Work Lost Due to PEP Side Effects	Number of days/Dead
Work Lost Due to Illness	Yes/No/Dead
Days of Work Lost Due to Illness	Number of days/Dead
Day of Relapse	Day after exposure/NA
Chronic Tularemia	Yes/No

The "Graphs" tab outputs a summary of the outcomes for all exposed individuals by compiling the data reported on the "Outputs" tab. Outcomes reported on the "Graphs" tab include the total number of exposed individuals, the number who develop symptoms, the number who die, the number of individuals who lose work due to MCM adverse side effects, the total number of days of work lost due to MCM adverse effects, the number of individuals who lose work due to illness (not including dead), the total number of days of work lost due to illness, and the total number of individuals with chronic tularemia. The summary of outcomes for the total exposed population is presented in Table 5 below. The "Graphs" tab also includes a pie chart and several line graphs. The pie chart displays the percentage of individuals who did not experience symptoms, the percentage that recovered after illness, and the percentage that died. The line graphs show the time after exposure when individuals in the population first experience symptoms and when they die.

Table 5. Summary of Outcomes for the Exposed Population (Graphs Tab)
Total exposed
Sick
Dead
Number of individuals who lose work due to MCM side effects
Days of work lost due to MCM side effects
Number of individuals who lose work due to illness (not including dead)
Days of work lost due to illness
Total with chronic tularemia

The sections below outline how the user inputs selected for each individual contribute to the intermediate and/or final outcomes for that individual.

Exposure Inputs

As described by Curling et al, the likelihood of symptom onset and the length of the incubation period are both dose-dependent. Our model allows users to choose the inhaled dose (in number of organisms) for each modeled individual. Based on the calculations described by Curling et al (and summarized in our parameters section), our model calculates the likelihood of symptom onset and, in individuals who develop symptoms, the length of the incubation period. For example, if an individual inhales 10 organisms, our model gives that individual a 50% chance of developing symptoms. If that individual develops symptoms, their incubation period will be selected from a normal distribution with a mean of 5.72 days and a standard deviation of 0.73 days. In addition, in individuals that receive the LVS vaccine the inhaled dose also affects the chance that a vaccinated individual will develop symptoms, as well as the severity and outcome of disease.

Vaccine Inputs

For each modeled individual, users can select whether that individual is vaccinated ("Yes") or not vaccinated ("No"). If vaccination is selected, the probability of an individual becoming ill is reduced according to a lognormal function that is dependent on the dose inhaled. Vaccination will also increase the length of the incubation period by one day as compared to the incubation period calculated if the individual were left unvaccinated. Vaccination can also affect the disease severity and outcome. Vaccinated individuals may experience mild disease (rather than typical) with an accompanying shortened symptomatic period, depending on the inhaled dose.

PEP Inputs

The PEP inputs include the first day that PEP is available and the duration of PEP. PEP affects the likelihood of developing symptoms in individuals who receive PEP before the time that symptom onset would otherwise occur. During the time period when PEP is taken, there is no chance an individual will develop symptoms since the efficacy of PEP while on antibiotics is 100%. After PEP is discontinued, the chance of developing symptoms is determined by a function (described in the "Efficacy of PEP after antibiotics are discontinued" section) that is dependent on the duration of the PEP antibiotics. For

example, when PEP is administered to an individual before the onset of symptoms for a period of five days, that individual will not fall ill for the duration of antibiotics but will have a 68% chance of falling ill after PEP is discontinued (because PEP was administered less than the recommended duration of 14 days).

Individuals who develop symptoms after PEP is discontinued will develop a less severe form of the disease and the likelihood of death is decreased to 7.5%. The timing of symptom onset and length of the symptomatic period in these individuals is calculated as if the individual inhaled five organisms after PEP was discontinued.

The PEP inputs also affect additional outcomes in individuals that survive. A subpopulation of non-symptomatic individuals that receive PEP will experience adverse effects from the antibiotics and therefore lose work even if they never display symptoms of tularemia. Loss of work due to PEP is calculated only for individuals who do not develop symptoms.

Treatment Inputs

For each modeled individual, users can choose if treatment will be available should the patient develop symptoms ("Yes" or "No") and, if applicable, what day after onset of symptoms treatment becomes available. The efficacy of treatment is affected by the day that treatment is made available in relation to the untreated time of death. As described in the "Parameters" section of this document, in order to be effective treatment must be made available before death, and early treatment has a higher efficacy than late treatment. The timing of treatment is combined with each individual's time of symptom onset and time of death to determine the likelihood of survival. For example, consider an untreated individual with symptom onset five days after exposure, and a time of death 12 days after exposure. If treatment is made available to this individual on any day through the tenth day after exposure the individual will survive. If treatment is made available 11 days after exposure then the individual will have a 50% chance of survival, and if treatment is made available 12 days after exposure (the day of death) then the individual will not survive.

The treatment inputs also affect additional outcomes associated with survivors. First, individuals that are treated with antibiotics and survive have a chance of relapsing after treatment. In addition, treated individuals may have an altered symptomatic period since their period of fever may be decreased due to the treatment. Likewise, since the number of days of work lost due to illness in individuals that recover is related to the period of fever, treatment also indirectly affects the number of days of work lost.

Excel Model Computational Framework

The *F. tularensis* MCM model is coded in Microsoft Excel. The model uses the previously described parameters to arrive at outcomes for each individual. The model is built in steps, where each step is represented by a calculation tab in the Excel workbook. For ease of use, the calculation tabs are hidden from the user.[113] The first step calculates the outcome for each individual with no MCM. The second step adds the effects of the vaccine inputs. Step three incorporates the effects of the PEP parameters, and step four incorporates the effects of the treatment parameters. The outputs for each individual's symptoms, time of symptom onset, period of fever, mortality outcome, and time to death are drawn from this tab. Step five calculates additional outcomes, including the days of work lost, and the presence or absence of

[113] Advanced users can access the calculation tabs by right clicking on any tab, selecting "Unhide" and choosing the tab that they wish to view.

adverse effects. Below we provide additional detail on the computational framework on each of these tabs as well as the connections between parameter calculations within the model.

Use of Random Number Generators

Many of the parameters established in the previous section give outcomes in the form of probabilities. Since the tularemia MCM model calculates values for individuals, the model uses a random number generator to determine whether or not a given outcome is realized for a particular individual. For example, our parameter section indicates that 5% of survivors will experience chronic tularemia. For every survivor we generate a random number greater than or equal to zero and less than or equal to one. If the random number is less than or equal to 0.05 the individual develops chronic tularemia. If the random number is greater than 0.05, that individual does not develop chronic tularemia. The random number generator thereby allows us to convert the probability of an event into a specific outcome for an individual. Incorporating this element of randomness allows us to model the many possible outcomes that one single individual may experience, and allows for a practical way of varying the outcomes of multiple individuals with identical input scenarios.

Additionally, the model's use of random numbers is designed to keep the results of each calculation step consistent for a single individual; therefore, each individual is assigned a single random number for each outcome that is reliant on a random number. For example each individual has a single random number associated with developing symptoms. If that random number is 0.6 and the chance of developing symptoms without vaccination is 98.97%, then individual will develop symptoms. With vaccination, the chance of developing symptoms falls to 35.6%; since the random number associated with developing symptoms is static for each individual, with treatment this individual will remain symptom free.

Step 1: No MCM

Using the exposure data input by the user, the model calculates each individual's outcome if no MCMs are administered. The outcomes established in this tab are based on those developed by Curling et al for disease in individuals who receive no MCM.[114] In the absence of MCM, the likelihood of symptoms and the likelihood of death are dependent on the dose indicated by the user. The likelihood of getting symptoms is a dose-dependent lognormal distribution, and the model determines whether or not each individual experiences symptoms by pairing the distribution with a random number generator. If the model determines that an individual develops symptoms, a second random number is used to convert the probability death (75%) into a final mortality outcome (survival or death). Given the final mortality outcome, the model calculates the duration of Stage 1 and the duration of Stage 2 by again combining the distribution of each stage (a normal distribution) with random numbers. The model calculates the length of fever by summing the duration of Stage 1 and Stage 2. If the individual dies, the model then calculates the day of death by summing the incubation period, Stage 1, and Stage 2. Death occurs on the last day of symptoms.

Step 2: Vaccine

If the user indicates that no vaccine is administered (by selecting "NA"), no change is made to the modeling outcomes in this step. If the user selects vaccination, the model adjusts the probability of developing symptoms. The exact probability of developing symptoms after vaccination depends on the dose of the agent (as described in the parameters section). A random number is once again used to convert

[114] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

the dose-dependent probability of symptoms into an outcome (sick or not sick). Other disease course outcomes are also affected by vaccination. First, the incubation period calculated in Step 1 is increased by one day. In addition, some vaccinated individuals may experience Mild Type 1 or Mild Type 2 disease rather than the typical disease. The chance of getting a mild form of the disease is dependent on dose, and again a random number is used to convert these probabilities into outcomes. Individuals who experience a mild form of the disease also have a shorter duration of Stage 1, and recover without experiencing any Stage 2 symptoms; therefore, the duration of fever is also shorter. In addition, all individuals with mild disease survive even in the absence of treatment. Once all adjustments have been made for vaccination, outcomes are recalculated using the same method applied in Step 1.

Step 3: PEP

If the user indicates that PEP is not administered by selecting "NA" or PEP is first made available after the day of symptom onset, no change is made to the modeling outcomes in this step. If the first day PEP is made available is before the day the model calculates for symptom onset, the model adjusts the probability of developing symptoms. During the period of PEP administration, no symptoms will develop. After PEP is discontinued, the exact probability of developing symptoms depends on the number of days that PEP was given (as described in the parameters section). A random number is once again used to convert the probability of symptoms into an outcome (sick or not sick).

If the individual does develop symptoms after discontinuing PEP, the severity of illness is reduced and the mortality rate is decreased to 7.5%. The time of symptom onset is calculated by adding the period from exposure to the discontinuation of PEP to the post-PEP incubation period (the period from discontinuation of PEP to symptom onset). The duration of the post-PEP incubation period and the duration of the symptomatic period is calculated as if the individual were exposed to five organisms of *F. tularensis* at the time when PEP was discontinued. Once all adjustments have been made for PEP, outcomes are recalculated using the same method applied in Step 1.

Step 4: Treatment

The treatment tab is the final step in determining disease-related outcomes for each individual. No outcomes are adjusted for individuals who receive no treatment; furthermore, the sick/not sick outcome is not adjusted during this step. The likelihood of death, however, is adjusted for individuals who receive timely treatment. If treatment is administered after the time of death, or after fever has subsided, treatment inputs are ignored. The model determines the exact probability of death by combining the time of treatment with the time of death if the individual were otherwise untreated (as described in the "Parameters" section). As before, the probability of death is converted into an actual outcome (recovery or death) using a random number generator. In individuals who would have lived even without treatment, treatment has no effect on the probability of death.

Individuals that are treated and survive have a 2% chance of experiencing relapse after treatment is complete. A random number generator is used to convert this probability into an outcome for each individual. If the individual experiences relapse, the timing of relapse is determined by a lognormal distribution. As before, a random number is used to place the individual on the distribution at random to determine the time until relapse. The model calculates the day of relapse by adding the incubation period, the duration of symptoms before antibiotics began, the ten days of antibiotic treatment, and the time until relapse, as described in the parameters section of this document.

Step 5: Work Lost in Individuals Who Survive

If an individual's outcome is death, Step 5 is not calculated. If an individual's outcome is survival, the model calculates outcomes for work lost due to PEP and/or illness as applicable. Individuals who receive PEP but do not develop symptoms have a chance of losing work due to adverse side effects of the prophylactic antibiotics. A random number generator is used to determine if an individual loses zero, one, two, three, or seven days of work due to PEP. For individuals that develop symptoms and recover, the model multiplies the days of fever experienced by 217% (SD 45%) to determine the days of work lost due to illness. Individuals that experience a modified symptomatic period, like vaccinated individuals that develop mild disease, will have a correspondingly fewer lost days of work due to their shorter period of fever. Finally, any treated individual that develops symptoms and then goes on to relapse will experience an additional 14 days of work lost due to illness.

Sample Results

This model of MCM efficacy against *F. tularensis* allows the user to input any combination of dose, pre-exposure, and post-exposure medical countermeasures for each individual modeled. Below we provide results from a few sample runs to demonstrate the range of outcomes the model will produce with varying inputs. The outcomes of each scenario include pie graphs divided into three categories: the "Not Sick" portion indicates the individuals that were exposed but did not develop symptoms; the "Recovered" portion indicates the individuals that developed symptoms and survived; the "Dead" portion indicates the individuals that developed symptoms and died. As mentioned previously, the model calculates each individual's outcome stochastically, so that each time the model is run, the output may differ even if the input parameters do not change.

Dose Variation (No MCM)

Here, the outcomes of three doses are compared. In each scenario, the individuals are exposed to varying doses of *F. tularensis* and receive no MCM. In scenarios one, two, and three, each individual is exposed to 1, 10, and 100 organisms respectively. Since these outputs do not include MCM, the outputs are based solely on the parameters described by Curling et al.

Input

Table 6. Input for Exposure to Varying Doses of *F. tularensis* - Modeling Example

	Scenario 1	**Scenario 2**	**Scenario 3**
Number of exposed individuals	500 individuals	500 individuals	500 individuals
Inhaled dose per person	1 organism	10 organisms	100 organisms
Vaccine	No	No	No
PEP	No	No	No
Treatment	No	No	No

Output

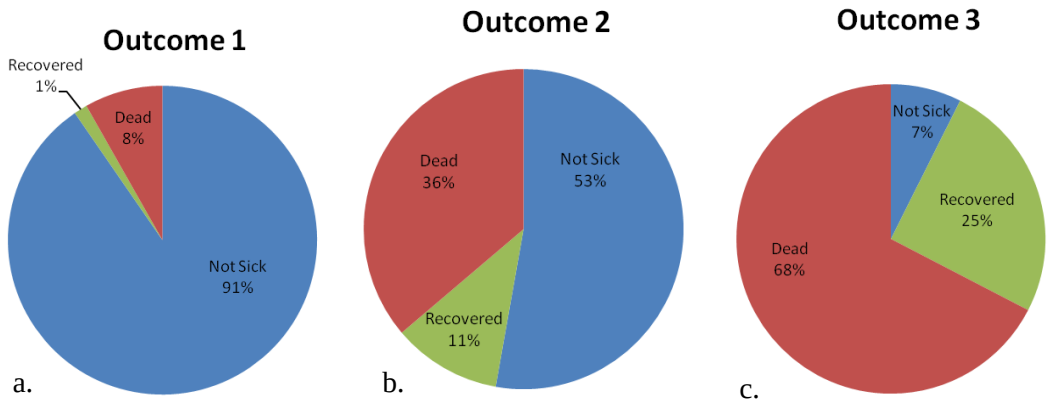

Figure 32. Outcomes for individuals exposed to (a) 1 (b) 10 or (c) 100 oraganism(s) of *F. tularensis* receiving no MCM.

Analysis

These results show that individuals exposed to small doses of agent may not develop symptoms at all. As the dose of inhaled agent increases, so does the likelihood that each individual will develop symptoms. According to Curling et al.,[115] symptomatic individuals have a 75% chance of death regardless of dose. In scenario one, a large percentage of exposed individuals do not develop disease, because the dose is relatively small. As the dose increases, more individuals are infected and, therefore, the outcome includes a larger number of deaths.

Vaccination

Vaccination with LVS can prevent the onset of symptoms. However, the level of protection after vaccination is dependent on dose; the larger the dose of agent a vaccinated individual inhales, the greater the chance that individual will develop symptoms. In this section, three modeling outputs are compared. In the first scenario, unvaccinated individuals are exposed to 1,000 organisms of *F. tularensis*. This scenario serves as a baseline for comparison with scenario two, where vaccinated individuals were exposed to 1,000 organisms of *F. tularensis* (the same dose as in scenario one). In the third scenario vaccinated individuals were exposed to 10,000 organisms of *F. tularensis*, 10 times the dose given in scenario two.

Input

Table 7. Input for Pre-exposure Vaccination - Modeling Example			
	Scenario 1	**Scenario 2**	**Scenario 3**
Number of exposed individuals	500 individuals	500 individuals	500 individuals
Inhaled dose per person	1,000 organisms	1,000 organisms	10,000 organisms

[115] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

Table 7. Input for Pre-exposure Vaccination - Modeling Example			
	Scenario 1	**Scenario 2**	**Scenario 3**
Vaccine	No	Yes	Yes
PEP	No	No	No
Treatment	No	No	No

Output

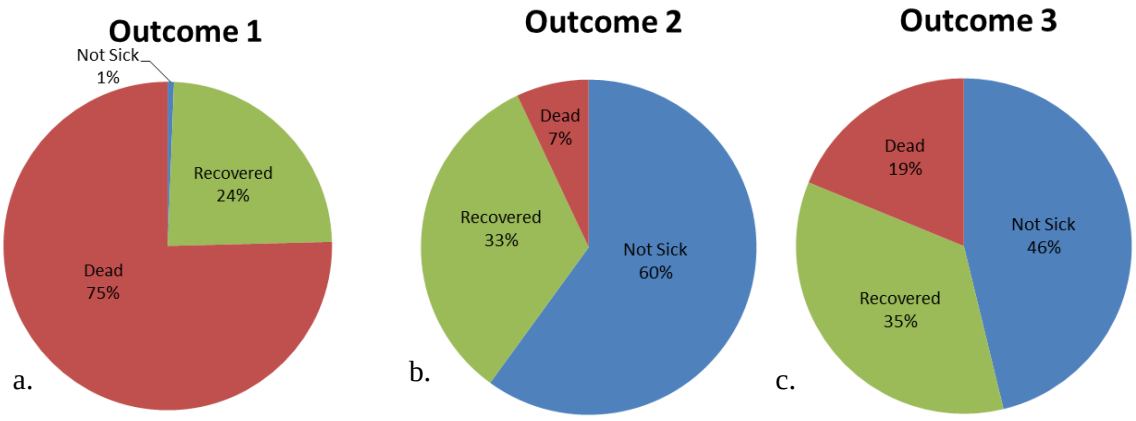

Figure 33. Outcomes for (a) unvaccinated individuals exposed to 1,000 *F. tularensis* organisms, (b) vaccinated individuals exposed to 1,000 *F. tularensis* organisms and (c) vaccinated individuals exposed to 10,000 *F. tularensis* organisms.

Table 8. Total Days of Work Lost Due to Illness		
Outcome 1	**Outcome 2**	**Outcome 3**
10,452 days (120 individuals)	4,020 days (165 individuals)	6,138 days (175 individuals)

Analysis

The model output demonstrates that the vaccine can prevent the onset of symptoms, but is less effective when individuals are exposed to larger doses of agent. The outputs also show that vaccinated individuals that develop symptoms are more likely to survive than unvaccinated individuals. The "work lost due to illness" output provides information about differences in severity of the disease experienced by vaccinated and unvaccinated individuals. Scenarios one and two have only a 9% difference in the number individuals that recover from the illness. However, the two scenarios have over a 250% difference in the total days of work lost due to illness (the sum of the days of work lost by each individual). This result is a consequence of the fact that vaccinated individuals often experience a less severe form of the disease and are therefore able to return to work sooner than unvaccinated individuals.

Though not shown here, the modeling output also accounts for a one day longer incubation period in vaccinated individuals that contract tularemia than in unvaccinated individuals that contract the disease.

Treatment with Antibiotics

In this example, we compare three scenarios in which individuals are exposed to *F. tularensis* and receive no MCM until after they develop symptoms. In scenarios one, two and three, each individual receives antibiotics starting one, ten or thirty days after symptoms begin.

Input

Table 9. Input for Treatment with Antibiotics - Modeling Example			
	Scenario 1	**Scenario 2**	**Scenario 3**
Number of exposed individuals	500 individuals	500 individuals	500 individuals
Inhaled dose per person	100,000 organisms	100,000 organisms	100,000 organisms
Vaccines	No	No	No
PEP	No	No	No
Treatment	Antibiotics available 1 day after the onset of symptoms	Antibiotics available 10 days after the onset of symptoms	Antibiotics available 30 days after the onset of symptoms

Output

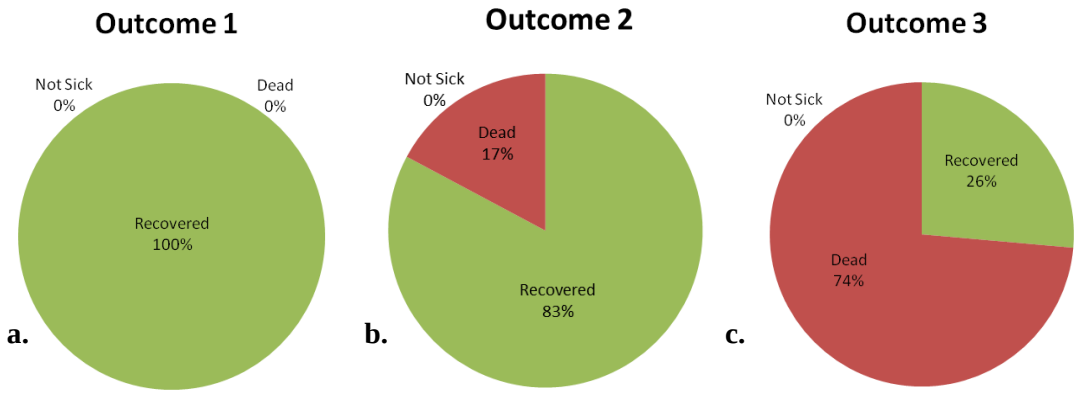

Figure 34. Outcomes for individuals exposed to 100,000 organisms of *F. tularensis* for whom antibiotics are available (a) one, (b) ten or (c) thirty days after the onset of symptoms.

Analysis

As shown above, when antibiotics are available one day after the onset of symptoms, individuals are nearly guaranteed to survive the infection. Even when treatment is delayed by more than a week, the majority of individuals survive; however, delaying treatment for a month provides little if any benefit given that the death rate for inhaled tularemia in individuals who receive no MCM is 75%, approximately the same death rate seen in scenario three.

Antibiotic PEP (Varied Start Time)

Antibiotic post-exposure prophylaxis can prevent the onset of symptoms; however, to be effective the antibiotics must be initiated before symptoms appear. In the scenario presented below, antibiotics are administered only as PEP and not as treatment. This means that although antibiotics may be available for use as PEP, they are not available for treatment. While this scenario is unrealistic, it demonstrates the importance of timely distribution of PEP antibiotics in preventing the onset of illness.

Input

Table 10. Input for PEP with Antibiotics (Varying Start Time) - Modeling Example			
	Scenario 1	**Scenario 2**	**Scenario 3**
Number of exposed individuals	500 individuals	500 individuals	500 individuals
Inhaled dose per person	100,000 organisms	100,000 organisms	100,000 organisms
Vaccines	No	No	No
PEP	Available 1 day after exposure; continued for 14 days	Available 2 days after exposure; continued for 14 days	Available 3 days after exposure; continued for 14 days
Treatment	No	No	No

Output

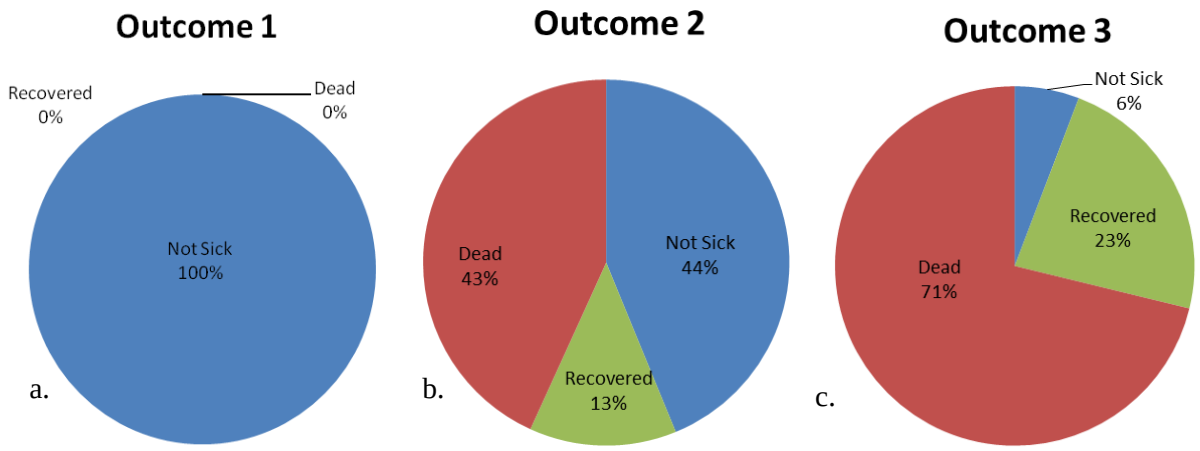

Figure 35. Outcomes for individuals exposed to 100,000 *F. tularensis* organisms that take a 14 day course of PEP beginning (a) one, (b) two or (c) three days after exposure.

Table 11. Days of Work Lost– Modeling Example			
	Outcome 1	**Outcome 2**	**Outcome 3**
Work lost from MCM	136 days (63 individuals)	71 days (32 individuals)	6 days (3 individuals)
Work lost from illness	0 days	5,806 days (65 individuals)	9,328 days (115 individuals)

Analysis

The pie charts above show how delaying the start of antibiotic PEP by even a few days will increase the number of individuals that develop disease. While PEP was 100% effective at preventing the onset of symptoms when initiated one day after exposure, delaying administration of PEP until three days after exposure almost completely eliminated its efficacy and nearly all those exposed became symptomatic. In this example, there was no post-symptomatic treatment; therefore, based on the parameters established by Curling et al, approximately 75% of symptomatic individuals died of the disease. With a lower dose of organisms, delaying PEP would have less of an effect. This is because the period in which PEP is effective (the incubation period) is typically longer in individuals exposed to lower doses of organisms; however, delaying PEP will still result in increased casualties. The model predicts that a percentage of the individuals that receive antibiotic PEP will have an adverse reaction to the drugs and lose work as a result. In scenario one in which antibiotic PEP was available beginning the day after exposure, the model predicts that a relatively large number of days of work will be lost due to MCM when compared with scenarios two and three. This is because all of the individuals in scenario one received PEP whereas only some of the individuals in scenarios two or three received PEP, since many of those individuals in these scenarios developed symptoms before PEP could be administered.

Because a negative reaction to the antibiotics may result in a loss of more than one day of work, the number of days of work lost is not equal to the number of individuals who lose work. In addition to days of work lost due to MCM, our model also accounts for work lost by individuals who develop symptoms and recover. Therefore, the number of days of work lost from illness is correlated to the number of individuals who recover. This is reflected in scenarios two and three above in which more days of work are lost from illness because more individuals were infected and became ill before recovering.

Antibiotic PEP (Varying Duration)

The efficacy of PEP antibiotics is dependent both on when they are first administered and the length of time they are taken. The example below demonstrates how prematurely discontinuing prophylaxis affects casualties. As in the previous example, this scenario, which assumes that antibiotics are administered solely as prophylaxis and not treatment, is intended to demonstrate only the effect of varying the duration of PEP. Thus, antibiotics are not available for treatment of symptomatic individuals.

Input

Table 12. Input for PEP with Antibiotics (Varying Duration) - Modeling Example			
	Scenario 1	**Scenario 2**	**Scenario 3**
Number of exposed individuals	500 individuals	500 individuals	500 individuals
Inhaled dose per person	100,000 organisms	100,000 organisms	100,000 organisms
Vaccines	None	None	None
PEP	Available 1 day after exposure; continued for 14 days	Available 1 day after exposure; continued for 7 days	Available 1 day after exposure; continued for 3 days
Treatment	No	No	No

Output

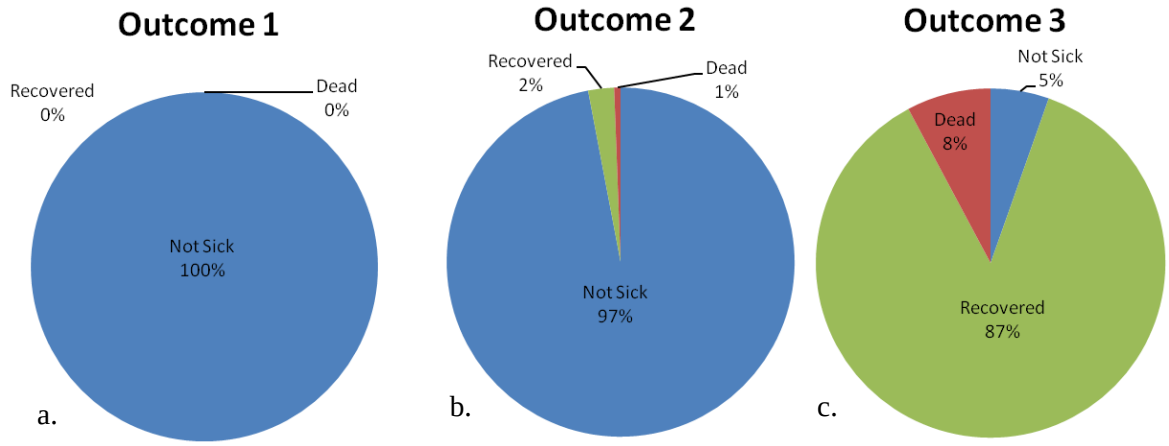

Figure 36. Outcomes for individuals exposed to 100,000 *F. tularensis* organisms that take a (a) 14 day, (b) 7 day or (c) 3 day course of PEP available one day after exposure.

Analysis

Figure 36 above demonstrates two changes that take place when PEP antibiotics are discontinued prematurely. The first noteworthy outcome is that the sooner PEP antibiotics are discontinued, the greater the number of individuals that develop symptoms. The second is that those individuals who develop symptoms after a truncated course of PEP are more likely to recover from illness than those who do not receive any PEP. Indeed, while the mortality rate in individuals who receive no MCM is approximately 75%, outcome three demonstrates that this mortality rate falls significantly in individuals who receive PEP.

Run to Run Variation

Our model of the efficacy of various countermeasures against *F. tularensis* is probabilistic and stochastic. The outcome for each individual is established using evidence-based parameters, probability distributions, and an element of randomness, which determines where in the probability distribution an individual falls. Therefore, two individuals with identical characteristics may experience different outcomes in the model. Specifically, given a description of agent exposure, PEP, vaccination, or treatment, the model calculates the likely outcome in terms of morbidity, mortality and loss of productivity due to illness and/or PEP adverse effects as applicable. The evidence-based parameters underlying the model determine the probability of each outcome; the model then uses a random number to convert this probability into an outcome for each individual.

Because the model incorporates an element of randomness, there is run-to-run variability in the outcomes. The extent of this variation is closely tied to the parameters that define each input scenario. Scenarios with parameters for which the probability of an event is 0% and scenarios with parameters for which the probability is 100% will have no variation in the outcome, since any random number drawn by the model will give the same outcome. As with a coin toss, each random number draw is independent of the previous draw. For example, it is possible (if unlikely), that ten people in a row will remain symptom-free following inhalation of *F. tularensis* bacteria, even if each has a 50% chance of developing symptoms. Figure 37 demonstrates that the closer the predicted chance of symptoms is to 50%, the greater the standard deviation between runs of 100 identical individuals.

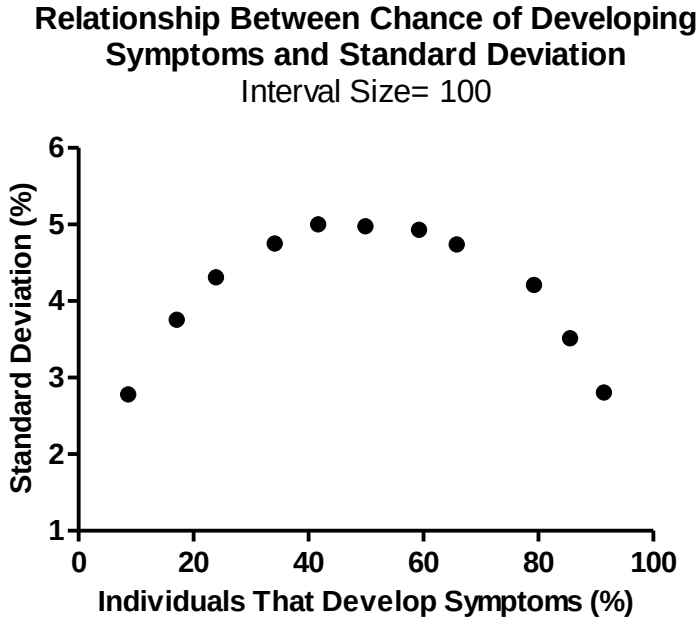

Figure 37. The relationship between the probability of symptom development and the standard deviation in outcomes, within a population of 100 individuals.

Users can reduce the standard deviation of the outcome by running the model for larger populations of individuals. For example, at its most variable (a probability of developing symptoms rate of 50%, a dose

of 10 organisms [116]), the standard deviation of the symptom rate in a model run with 100 individuals is 5%, but drops to 1% with 10,000 individuals. Table 13 below demonstrates how, in an example model run, the standard deviation decreases as the number of identical people increases.

Table 13. Effect of Population Size on Standard Deviation			
# of individuals	**100**	**1,000**	**10,000**
Mean # symptomatic individuals	49.92	499.27	4992.73
SD (people)	4.98	16.37	53.76
SD (%)	5%	2%	1%
Scenario - Inhaled Dose: 10 organisms; Vaccination: None; PEP: None; Treatment: None			

Modeling runs that contain few identical individuals are likely to have significant run-to-run variation. Users who wish to produce outcomes closer to the average should take the mean of a large number of individuals with identical inputs, either by running many individuals at once or taking the average of several identical runs.

[116] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

Conclusions

The Microsoft Excel *F. tularensis* model described in this work estimates the morbidity, mortality, course of disease, and work lost in individuals following exposure to aerosolized *F. tularensis*. The model was built using No MCM disease course parameters developed by Curling et al[117], and evidence-based countermeasure efficacy parameters developed by Gryphon Scientific. This model is intended to be used as a tool to estimate outcomes and determine needs in a military population exposed to aerosolized *F. tularensis*. Using this model, military planners can better understand the vulnerabilities of warfighters, the benefit of countermeasures, and logistical tradeoffs on the battlefield.

[117] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

Appendix 1. Incubation Period

Curling et al. report that the incubation period for tularemia is a function of dose (number of *F. tularensis* organisms to which an individual is exposed), but they report no standard deviation for this value.[118] Table A-1 below reports the raw data we used to calculate the 0.73 day standard deviation associated with the incubation period. It is important to note that the standard deviation was calculated based on the limited data set available, and it is assumed to be applicable at the broader range of exposure doses included in the Curling et al calculation of the incubation period.

Table A-1. Raw Dose and Incubation Period Data from Saslaw et al.[119] Used to Determine the Standard Deviation of the Incubation Period

	Challenge Dose	Incubation Period
Dose Group 15	10	6
	13	7
	14	5
	15	6
	16	6
	18	5
	Standard Deviation	*0.75 days*
Dose Group 25	20	7
	23	6
	23	5
	25	5
	30	5
	Standard Deviation	*0.89 days*
Dose Group 50	46	4
	46	4
	48	5
	50	4
	52	5
	Standard Deviation	*0.55 days*
	Average Standard Deviation	***0.73 days***

[118] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

[119] Saslaw S. et al. "Tularemia Vaccine Study II. Respiratory Challenge." *Archives of Internal Medicine*. **107.** 1961.

Appendix 2. Symptomatic Periods

Curling et al. report that the lengths of Stage 1 and Stage 2 symptomatic periods for tularemia were established using data from Stuart and Pullen, but no standard deviation values were calculated.[120] Table A-2 shows the raw data, as presented by Curling et al,[121] that were used to estimate a standard deviation for Stages 1 and 2 in individuals that survived and in those that died.

Table A-2. Raw Data from Stuart and Pullen as Presented in Curling et al

Case	Duration of Symptoms Before Pneumonia in Days (Stage 1)	Duration of Pneumonia in Days (Stage 2)
Survivor #1	14	33
Survivor #2	10	22
Survivor Average/SD	*Avg: 12 / SD: 2.8*	*Avg: 28 / SD: 7.8*
Fatality #1	10	5
Fatality #2	6	4
Fatality #3	8	2
Fatality #4	8	2
Fatality #5	12	5
Fatality #6	9	19
Fatality Average/SD	*Avg: 9 / SD: 2.0*	*Avg: 6 / SD: 6.4*

[120] Stuart BM and Pullen RL. "Tularemic pneumonia. Review of American literature and report of 15 additional cases." *Am Med Sci.* **210**(2). 1945.

[121] Curling CA et al. "Parameters for Estimation of Casualties from Exposure to Specified Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia: Volume 1" IDA Document D-4132. November 2010.

Appendix 3. Vaccination

Efficacy

A series of tularemia vaccine challenge studies were published in the 1960s. Data from studies involving respiratory challenge of human volunteers vaccinated via acupuncture or scarification with a live attenuated strain (like LVS) of *F. tularensis* were used to establish our efficacy parameter and are presented in Table A-3 below.

Table A-3. Efficacy of Viable Vaccine Administered via Scarification in Individuals Challenged with Aerosolized *F. tularensis*

Challenge dose	Percent of Control group that developed fever (# with fever/total in in group)	Percent of Vaccinated group that developed fever (# with fever/total in in group)	Vaccine Efficacy	Reference
11 (10-13)	50% (2/4)	0% (0/6)	100%	Saslaw et al. 1961[122]
25 (23-26)	100% (2/2)	25% (1/4)	75%	Saslaw et al. 1961
48 (46-53)	100% (4/4)	25% (2/8)	75%	Saslaw et al. 1961
200	100% (2/2)	17% (1/6)	83%	McCrumb 1961[123]
2,000	100% (2/2)	40% (2/5)	60%	McCrumb 1961
2,500	100% (2/2)	13%(1/8)	87%	Pekarek et al. 1969[124]
20,000	100% (2/2)	100% (3/3)	0%	McCrumb 1961
25,000	94% (44/47)	63% (29/46)	33%	Hornick and Eigelsbach 1966[125]
25,000	100% (2/2)	70% (7/10)	30%	Pekarek et al. 1969

Vaccine Effect on Disease Severity and Outcome

A number of human studies (described in Table A-4 below) indicate that some individuals who developed tularemia despite vaccination experienced a milder illness than the positive controls. This reduction in severity of symptoms appeared to be dose dependent. The studies listed in Table A-4 below show the

[122] Saslaw S. et al. "Tularemia Vaccine Study II. Respiratory Challenge." *Archives of Internal Medicine*. **107.** 1961.
[123] McCrumb FR. "Aerosol Infection of Man with Pasteurella Tularensis" *Bacteriol Rev*. **25**(3). 1961.
[124] Pekarek RS et al. "The Effects of Francisella Tularensis Infection on Iron Metabolism in Man". *American Journal of the Medical Sciences*. **258**(1). 1969.
[125] Hornick RB and Eigelsbach HT. "Aerogenic Immunization of Man with Live Tularemia Vaccine." *Bacteriological Reviews*. **30**(3). 1966.

relationship between dose of organisms and the number of symptomatic individuals who experienced mild rather than typical tularemia. These human studies were used to develop an equation for the likelihood of a vaccinated, symptomatic individual to develop mild symptoms as a function of dose: $Z_{mild} = (1.6980 - 0.2948 \log(D_0))$. Figure A-1 shows the data supporting this assertion graphically and the equation of the line used to model this effect.

Table A-4. Relationship Between Dose of Agent and Number of Symptomatic Vaccinated Individuals Who Experience Mild (Rather Than Typical) Tularemia

Dose Group	Dose	Number of Vaccinated Symptomatic Individuals	Number Who Experienced Mild Symptoms or Did Not Require Treatment	Percent of Vaccinated Symptomatic Individuals Who Experienced Mild Symptoms	Reference
200	200	1	1	100%	McCrumb 1961[126]
2,250	2,000	2	2	75%	McCrumb 1961
	2,500	2	1		McCrumb 1961
23,333	20,000	3	2	39%	McCrumb 1961
	25,000	7	4		Pekarek 1969[127]
	25,000	29	8		Hornick and Eigelsbach 1966[128]

[126] McCrumb FR. "Aerosol Infection of Man with Pasteurella Tularensis" *Bacteriol Rev*. **25**(3). 1961.

[127] Pekarek RS et al. "The Effects of Francisella Tularensis Infection on Iron Metabolism in Man". *American Journal of the Medical Sciences*. **258**(1). 1969.

[128] Hornick RB and Eigelsbach HT. "Aerogenic Immunization of Man with Live Tularemia Vaccine." *Bacteriological Reviews*. **30**(3). 1966.

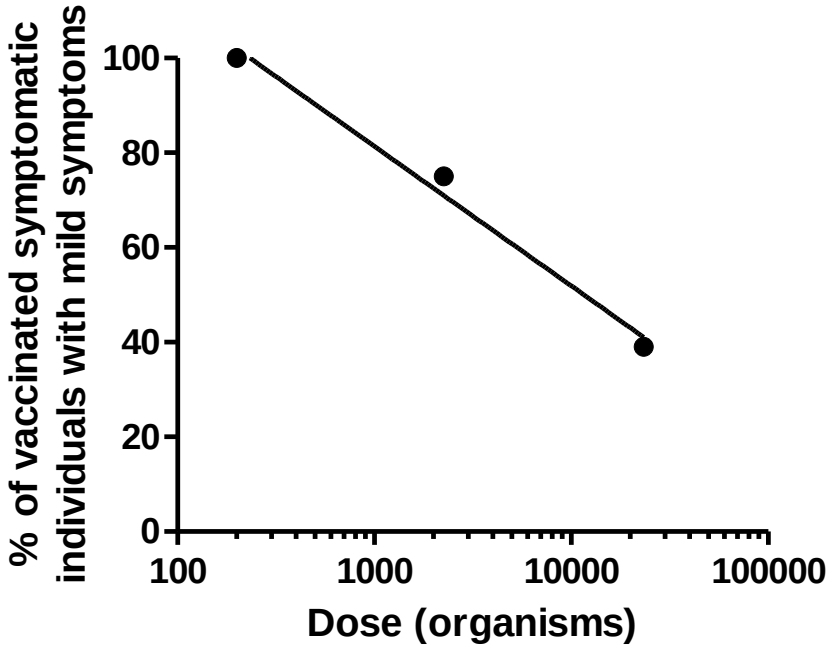

Figure A-1. Relationship between dose of *F. tularensis* and percent of vaccinated symptomatic individuals that have a mild (rather than typical) form of the disease. The equation representing this line is $Z_{mild} = 169.80 - 29.48 \log(D_0)$, where D_o is the inhaled dose of *F. tularensis.*

The McCrumb study described in Table A-4 found that vaccinated patients who developed mild disease after vaccination had varying levels of disease severity.[129] The least severe form of the disease (which we refer to as mild Type I) presented as a mild febrile disease, which remitted spontaneously in 24 to 48 hours. Other patients with mild symptoms (which we refer to as mild Type II) experienced an illness that persisted for more than 48 hours, but was less severe than the controls. We chose to include these two subcategories of mild illness in order to most accurately represent the altered symptomatic period after vaccination. We found that this subdivision of mild disease was dose-dependent. McCrumb studied the effects of vaccination at three challenge doses (20, 200 and 2,000 organisms) and found that mild Type I disease was experienced by all of the symptomatic vaccinated individuals challenged with 20 organisms and half of the symptomatic vaccinated individuals challenged with 200 organisms. The other half of the symptomatic individuals challenged with 200 organisms experienced mild Type II illness. This form of the disease was also experienced by all of the individuals challenged with 2,000 organisms who did not develop the typical disease. The equation of the line in Figure A-2 describes the percent of symptomatic individuals with a mild illness that develop a Type I (rather than Type II) disease as a function of the dose of *F. tularensis* to which they were exposed.

[129] McCrumb FR. "Aerosol Infection of Man with *Pasteurella Tularensis*" *Bacteriol Rev*. **25**(3). 1961.

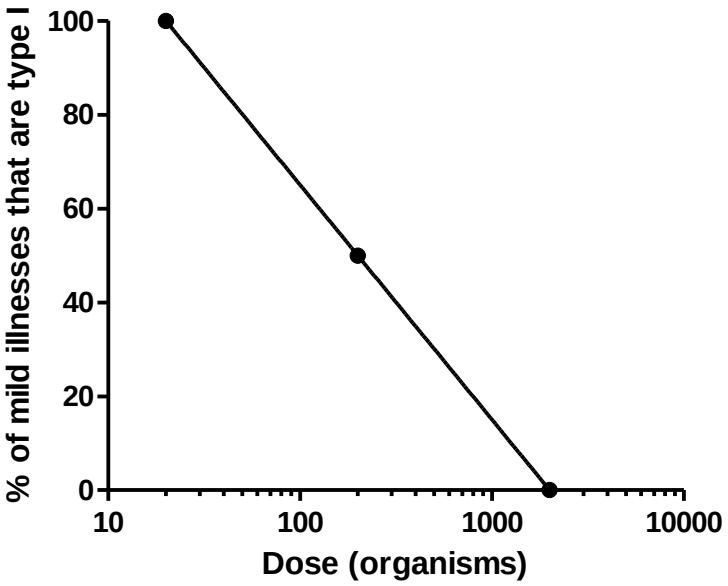

Figure A-2. Relationship between dose of *F. tularensis* and the percentage of mild symptomatic vaccinated individuals who develop type I rather than type II mild symptoms described by the equation: $\%\, \boldsymbol{Type\ Z = 1.651 - 0.50 * \log(D_0)}$**, where $\boldsymbol{D_0}$ is the inhaled dose of $\boldsymbol{F. tularensis}$.**

The equation described in Figure A-2 indicates the percentage of mild Type I cases out of the total number of mild cases. We used both the equation for the proportion of mild cases out of all symptomatic individuals (Z_{mild}) and the equation for the percent of Type I illness out of all mild cases to characterize the number of vaccinated symptomatic individuals that have mild Type I, mild Type II, and typical illness, as described by the equations below.

Percentage of symptomatic vaccinated individuals with any form of mild disease
If $(1.6980 - 0.2948\log(D_0)) < 0.00$, $Z_{mild} = 0\%$
If $(1.6980 - 0.2948\log(D_0)) > 1.00$, $Z_{mild} = 100\%$
Otherwise: $Z_{mild} = (1.6980 - 0.2948\log(D_0))$

Where:
D_o is the dose of agent
Z_{mild} = percentage of symptomatic individuals who develop any type of mild illness

Percentage of all symptomatic individuals that have Mild Type I
If $(1.651 - 0.50 * \log(D_0)) * Z_{mild} < 0.00$, Z_{MI} = 0%
If $(1.651 - 0.50 * \log(D_0)) * Z_{mild} > 1$, Z_{MI} = 100%
Otherwise: $Z_{MI} = (1.651 - 0.50 * \log(D_0)) * Z_{mild}$

Where:
D_o is the dose of agent
Z_{mild} = percentage of all symptomatic individuals who develop any type of mild illness
Z_{MI} = percentage of all symptomatic individuals who develop a mild Type I form of the disease

Percentage of all symptomatic individuals that have Mild Type II

$Z_{MII} = Z_{mild} - Z_{MI}$

Where:
Z_{mild} = percentage of all symptomatic individuals who develop any type of mild illness
Z_{MI} = percentage of all symptomatic individuals who develop a mild Type I form of the disease
Z_{MII} = percentage of all symptomatic individuals who develop a mild Type II form of the disease

Percentage of symptomatic vaccinated individuals with the typical form of the disease.

$Z_T = 1 - Z_{mild}$

Where:
Z_T = percentage of symptomatic individuals who develop a typical form of the disease
Z_{mild} = percentage of symptomatic individuals who develop any type of mild illness

Mortality outcome in symptomatic vaccinated individuals:
Mild Type I: Mortality rate = 0%
Mild Type II: Mortality rate = 0 %
Typical: Mortality rate = 75%

Appendix 4. Antibiotic Post-Exposure Prophylaxis (PEP)

Antibiotic PEP against tularemia is likely to be administered via oral ciprofloxacin or doxycycline.[130] Because the data on oral antibiotics were insufficient to completely characterize the parameter describing PEP efficacy, our analysis included studies of both oral and injected ciprofloxacin and doxycycline. Similarly, we considered data from both aerosol exposure and exposure by injection, because data from aerosol exposure alone was insufficient to adequately address the efficacy of PEP administered for various durations.

Data from animal studies were compared to information about human disease in order to best assess whether the animal data could be used to establish parameters describing human disease. When human data were insufficient or unavailable, data from studies in monkeys were used, since monkeys and humans experience similar clinical and pathological signs of tularemia. For example, both humans and monkeys experience fever in the very early stages of disease, and this symptom is used as a criterion of illness in both species.[131] Because mice do not experience fever when infected with *F. tularensis*, they are not an ideal model animal for this disease.[132] When data from mouse studies were required due to a lack of data from more relevant models, we turned to a study which listed indicators of symptoms in mice: huddling, ruffled fur, lethargy, and decreased mobility. These symptoms were observed between 24 and 48 hours after exposure.[133] Therefore, antibiotics administered to mice between 0 and 24 hours after exposure were considered to be post-exposure prophylaxis, not treatment.

Efficacy of PEP while on Antibiotics

Tetracycline prophylaxis in humans has been shown to be 100% effective in preventing symptoms after aerosol exposure to *F. tularensis* when administered for 14 days[134] (the CDC recommended duration for PEP).[135] Tetracycline administered as PEP was also 100% effective in preventing illness in four monkeys given 200 mg of tetracycline four times a day for 13 days, even though all four monkeys fell ill after PEP was discontinued.[136] Another human report describes laboratory workers inadvertently exposed to Type A *F. tularensis* and administered 100 mg of doxycycline twice daily for an unspecified duration. None of the eleven workers that received prophylaxis developed symptoms.[137,138] These human and monkey data indicate that neither humans nor animals develop symptoms while PEP is being administered. This conclusion is further supported by mouse studies: even when given inadequate doses of doxycycline PEP, infected mice survived for 14 days while the drug was administered, though they all died within 7 days

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130 Dennis DT et al. "Consensus Statement: Tularemia as a Biological Weapon: Medical and Public Health Management." *JAMA.* **285**(21). 2001. CDC. "Emergency Preparedness & Response: Tularemia, Treatment and PEP." July 1, 2005. http://www.bt.cdc.gov/agent/tularemia/tularemia-biological-weapon-abstract.asp#4. Accessed on April 1, 2011.

131 Lyons and Wu. "Animal models of *Francisella tularensis* infection." *Annals of the New York Academy of Sciences.* **1105**(1). 2007.

132 Lyons and Wu. "Animal models of *Francisella tularensis* infection." *Annals of the New York Academy of Sciences.* **1105**(1). 2007.

133 Russell P et al. "The efficacy of ciprofloxacin and doxycycline against experimental tularemia." *Journal of Antimicrobial Chemotherapy.* **41**(4). 1998.

134 Sawyer W et al. "Antibiotic prophylaxis and therapy of airborne tularemia." *Microbiology and Molecular Biology Reviews.* **30**(3). 1966.

135 CDC. "Tularemia: Abstract 'Consensus Statement' by Dennis et al." July 1 2005. http://www.bt.cdc.gov/agent/tularemia/tularemia-biological-weapon-abstract.asp#4. Accessed on May 19, 2011. Abstracted from: Dennis D et al. "Tularemia as a biological weapon: medical and public health management." *JAMA.* **285**(21). 2001.

136 One monkey with a concurrent illness other than tularemia was excluded from this analysis. Sawyer W et al. "Antibiotic prophylaxis and therapy of airborne tularemia." *Microbiology and Molecular Biology Reviews.* **30**(3). 1966.

137 One pregnant employee declined antibiotics but still did not develop symptoms.

138 Shapiro DS and Schwartz DR. "Exposure of laboratory workers to *Francisella tularensis* despite a bioterrorism procedure." *Journal of Clinical Microbiology.* **40**(6). 2002.

once PEP was discontinued.[139] Based on the collection of these data, we model PEP as 100% effective in preventing symptoms for the duration of antibiotic administration.

Efficacy of PEP after Antibiotics are Discontinued

Although the mechanisms of action of doxycycline and ciprofloxacin are different, both are effective as PEP against tularemia. Doxycycline, a bacteriostatic antibiotic, prevents replication of bacteria and relies on the immune system to clear the infection, while ciprofloxacin, a bacteriocidal antibiotic, kills the bacteria itself. While it might be expected that a bacteriocidal antibiotic such as ciprofloxacin would be more effective than a bacteriostatic antibiotic, we were unable to find enough data comparing the efficacy of the two drugs against tularemia to develop separate parameters. If more efficacy data become available, it would be prudent to establish separate parameters describing their efficacy as PEP. Table A-5 below describes the human data included in our analysis.

Table A-5. Human Antibiotic PEP

Source	Scenario	Antibiotic PEP	Results
Shapiro 2002[140]	Clinical: laboratory workers inadvertently exposed to patient specimens from a fatal Type A tularemia case	11 workers: Doxycycline 100 mg twice daily; duration not reported 1 worker: No antibiotic administered due to pregnancy; fever watch only	No employees developed symptoms
Sawyer 1966[141]	Experimental: Aerosol exposure to 25,000 organisms of virulent Type A *F. tularensis*	8 volunteers: Tetracycline 2 g/day for 14 days[142]	No volunteers developed symptoms

As described above, human data suggest that antibiotic PEP is 100% effective when administered for a full 14 days (the recommended duration of treatment). However, there are no human data on the efficacy of PEP when antibiotics are prematurely discontinued. Therefore, the parameter describing the likelihood of illness after various truncated courses of PEP is based on data from animal studies.

In considering animal studies, we assumed that if symptoms arose despite PEP, then the duration of antibiotics was insufficient to fully clear the bacteria from the host. However, when comparing animals to humans we must take into account the differences that may exist in the efficacy of antibiotics between species. We expect that the effect of the antibiotic on the bacteria itself would be similar between humans and other animals, since the antibiotic acts on the bacteria, not the host. However, the immune response to *F. tularensis* is likely different between animal species. In particular, the rate of clearance of bacteria

139 Steward J et al. "Treatment of murine pneumonic *Francisella tularensis* infection with gatifloxacin, moxifloxacin or ciprofloxacin." *International Journal of Antimicrobial Agents.* **27**(5). 2006.

140 Shapiro DS and Schwartz DR. "Exposure of laboratory workers to *Francisella tularensis* despite a bioterrorism procedure." *Journal of Clinical Microbiology.* **40**(6). 2002.

141 Sawyer W et al. "Antibiotic prophylaxis and therapy of airborne tularemia." *Microbiology and Molecular Biology Reviews.* **30**(3). 1966.

142 Other volunteers in this study were administered less efficacious doses of antibiotics, but since we assume that PEP will be administered at an adequate dose we have only considered the highest treatment regimen from this study.

after administration of doxycycline, which is bacteriostatic and therefore only prevents replication, would likely be different. Unfortunately, none of the studies uncovered by our team address species differences in either the immune response or in antibiotic action after antibiotic treatment, therefore we assume that the clearance rate is comparable between humans and animals. Table A-6 describes the animal data included in our analysis.

Table A-6. Antibiotic PEP Efficacy in Animals

Source	Animal	Antibiotic	Dose per Day	Duration (Days)	%Symptom-Free*
N/A	Assumed	N/A	N/A	1	0%
Russell 1998[143]	Mouse	Doxycycline	20 mg/kg	5	49%
Russell 1998	Mouse	Ciprofloxacin	20 mg/kg	5	71%
Russell 1998	Mouse	Doxycycline	40 mg/kg	5	77%
Russell 1998	Mouse	Ciprofloxacin	40 mg/kg	5	74%
Nelson 2010[144]	Monkey	Levofloxacin	33 mg/kg	10	100%
Peterson 2010[145]	Mouse	Levofloxacin	10 mg/kg	13	100%
Klimpel 2008[146]	Mouse	Levofloxacin	40 mg/kg	13	100%
Sawyer 1966[147]**	Monkey	Tetracycline	200 mg/day	13	0%**

**Percent without delayed onset of symptoms and/or death after antibiotic withdrawal.*
***This study was excluded from our analysis because approximately the same conditions were effective at preventing symptom onset in human volunteers (80% effective for once daily administration over 15 days, 100% for twice daily administration over 14 days) indicating that tetracycline prophylaxis was much less effective in monkeys than in humans.*

Sawyer et al., who showed experimentally that 14 days of tetracycline PEP was effective at preventing symptom onset in humans, conducted the same experiment in rhesus macaques.[148] Unlike the human subjects, tetracycline did not prevent tularemia symptoms in all of the tested monkeys, suggesting that antibiotic prophylaxis is more effective in humans than rhesus macaques.

143 Russell P et al. "The efficacy of ciprofloxacin and doxycycline against experimental tularemia." *Journal of Antimicrobial Chemotherapy.* **41**(4). 1998.

144 Nelson M et al. "Bioavailability and efficacy of levofloxacin against *Francisella tularensis* in the common marmoset (*Callithrix jacchus*)." *Antimicrobial Agents and Chemotherapy.* **54**(9). 2010.

145 Peterson JW et al. "Protection Afforded by Fluoroquinolones in Animal Models of Respiratory Infections with *Bacillus anthracis, Yersinia pestis,* and *Francisella tularensis.*" *The Open Microbiology Journal.* **4**. 2010.

146 Klimpel GR et al. "Levofloxacin rescues mice from lethal intra-nasal infection with virulent *Francisella tularensis* and induces immunity and production of protective antibody." *Vaccine.* **26**(52). 2008.

147 Sawyer W et al. "Antibiotic prophylaxis and therapy of airborne tularemia." *Microbiology and Molecular Biology Reviews.* **30**(3). 1966.

148 Sawyer W et al. "Antibiotic prophylaxis and therapy of airborne tularemia." *Microbiology and Molecular Biology Reviews.* **30**(3). 1966.

Nelson et al. demonstrated that levofloxacin, an antibiotic in the same class as ciprofloxacin, was 100% effective in preventing symptoms in marmosets when administered as PEP for 10 days.[149] Although marmosets and rhesus macaques are different species of monkeys, we assume that prophylaxis against tularemia in marmosets will be as effective or less effective (as seen in rhesus macaques) as it is in humans. Based on these monkey data, we assume that antibiotics administered to humans as PEP for 10 days are 100% effective at preventing symptom onset. Because we found no non-human primate data on the efficacy of PEP when administered for fewer than 10 days, we turned to data from studies in mice.

Our team found only one mouse study in which PEP antibiotics were administered for less than 10 days. Russell et al. tested the efficacy of administering either ciprofloxacin or doxycycline to mice for five days after injection of various doses of bacteria.[150] The results from this study showed that five days of antibiotic PEP was not completely effective, and a number of animals died. We used the data from animals given PEP for fewer than 14 days to show that a shortened duration of PEP will likely prevent symptom onset in some but not all individuals.

The data from the human and animal studies described above were used to fit a curve describing the chance that individuals will be symptom-free after PEP (main text Figure 21). We assumed that the efficacy of PEP for the shortest duration allowable in our model, one day, would not be effective in preventing symptom onset. Based on a regression analysis, the equation describing the chance of not developing symptoms after PEP ($E_{discontinued}$) used in our model is $E_{discontinued} = 100 \times {d_{PEP}}^{7.526} \div (8.6664 \times 10^4 + {d_{PEP}}^{7.526})$ where d_{PEP} is the duration of PEP in days. This shape of the sigmoidal curve is expected because there should be a point where the antibiotic duration is sufficient to completely kill bacteria and thus plateau to 100%, and a point where the duration is insufficient to completely kill bacteria and thus plateau to 0%. Further details on the studies that were included in our analysis are provided in Appendix 4.

[149] Nelson M et al. "Bioavailability and efficacy of levofloxacin against *Francisella tularensis* in the common marmoset (*Callithrix jacchus*)." *Antimicrobial Agents and Chemotherapy.* **54**(9). 2010.

[150] Although this study tested multiple doses of injected bacteria, there was only a very weak correlation between dose and antibiotic efficacy. Since the data were insufficient to analyze dose, we considered only the average efficacy over all tested doses. If more information becomes available on shortened durations of PEP and delayed onset, it would be worthwhile revisiting the relationship between dose and PEP efficacy.

Appendix 5. Treatment with Antibiotics

Animal Data

The data from the three animal studies[151,152,153] in which antibiotic treatment was initiated at various times after exposure are presented in Table A-7. Data were included only from studies in which the animals were exposed intranasally or by aerosol and treated with injected antibiotics administered at multiple time points after exposure. When the timing of treatment is compared to the mean time to death (MTTD) of control animals, both studies in mice fit well with our assumptions for human patients. In guinea pigs, antibiotic treatment was less effective than in either mice or humans, with a maximum reported treatment efficacy after early treatment of only 90% (versus 100% in mice and humans). The data from both guinea pig and mouse studies support our assessment that antibiotic treatment is very effective early in the symptomatic period, but decreases over the span of multiple days close to the time of death.

Table A-7 shows the efficacy of treatment at various times in relation to the MTTD of controls. The MTTD of control animals is expressed as time 0. Negative numbers indicate treatment initiated before the MTTD, and positive numbers indicate that treatment was initiated after MTTD in control animals (which occurred in only one circumstance, and was excluded from our final analysis).

[151] Klimpel GR et al. "Levofloxacin rescues mice from lethal intra-nasal infection with virulent *Francisella tularensis* and induces immunity and production of protective antibody." *Vaccine.* **26**(52). 2008.

[152] Peterson JW et al. "Protection Afforded by Fluoroquinolones in Animal Models of Respiratory Infections with *Bacillus anthracis, Yersinia pestis,* and *Francisella tularensis.*" *The Open Microbiology Journal.* **4.** 2010.

[153] Libich J. "Effect of the administration of streptomycin in the incubation and manifest phase on the course of inhalation tularemia in guinea pigs." *Folia Micobiologica.* **7.** 1962.

Table A-7. Efficacy of Antibiotics Versus Time of Treatment in Animal Models

Animal	Strain	Antibiotic	MTTD of Controls (Days)**	Treatment Time Post Exposure	Time Relative to MTTD (Days)	*F. tularensis* Dose*	Antibiotic Dose	Survival Rate	Source
Mouse	SCHU-S4	Levofloxacin	5.8	24 hrs	-4.8	100 CFU i.n.	40 mg/kg/day IP	100%	Klimpel 2008[154]
				48 hrs	-3.8	114 CFU i.n.	40 mg/kg/day IP	100%	
				72 hrs	-2.8	114 CFU i.n.	40 mg/kg/day IP	100%	
				96 hrs	-1.8	114 CFU i.n.	40 mg/kg/day IP	80%	
				120 hrs	-0.8	114 CFU i.n.	40 mg/kg/day IP	0%	
Mouse	SCHU-S4	Levofloxacin	4.95	24 hrs	-3.95	99 CFU i.n.	40 mg/kg/day IP	100%	Peterson 2010[155]
				48 hrs	-2.95	99 CFU i.n.	40 mg/kg/day IP	100%	
				72 hrs	-1.95	99 CFU i.n.	40 mg/kg/day IP	100%	
				96 hrs	-0.95	99 CFU i.n.	40 mg/kg/day IP	80%	
				120 hrs	+0.05	99 CFU i.n.	40 mg/kg/day IP	0%	
Guinea Pig	2713	Streptomycin	~7	24 hrs	-6	200-6500 CFU aerosol	5 mg, 2x daily IM	90%	Libich 1962[156]
				96 hrs	-3	200-6500 CFU aerosol	5 mg, 2x daily IM	75%	

Analysis excludes studies of orally administered drugs.
**Number of organisms.*
***Mean time to death of control animals.*

Figure A-3 graphically compares the data underlying our parametric values with the data derived from animal studies as described above. This parameter is based on the assumption, supported by the human and animal data described above, that antibiotic treatment is 50% effective one day before death and 0% effective on the day of death.

[154] Klimpel GR et al. "Levofloxacin rescues mice from lethal intra-nasal infection with virulent *Francisella tularensis* and induces immunity and production of protective antibody." *Vaccine.* **26**(52). 2008.

[155] Peterson JW et al. "Protection Afforded by Fluoroquinolones in Animal Models of Respiratory Infections with *Bacillus anthracis, Yersinia pestis,* and *Francisella tularensis.*" *The Open Microbiology Journal.* **4**. 2010.

[156] Libich J. "Effect of the administration of streptomycin in the incubation and manifest phase on the course of inhalation tularemia in guinea pigs." *Folia Micobiologica*. **7**. 2010.

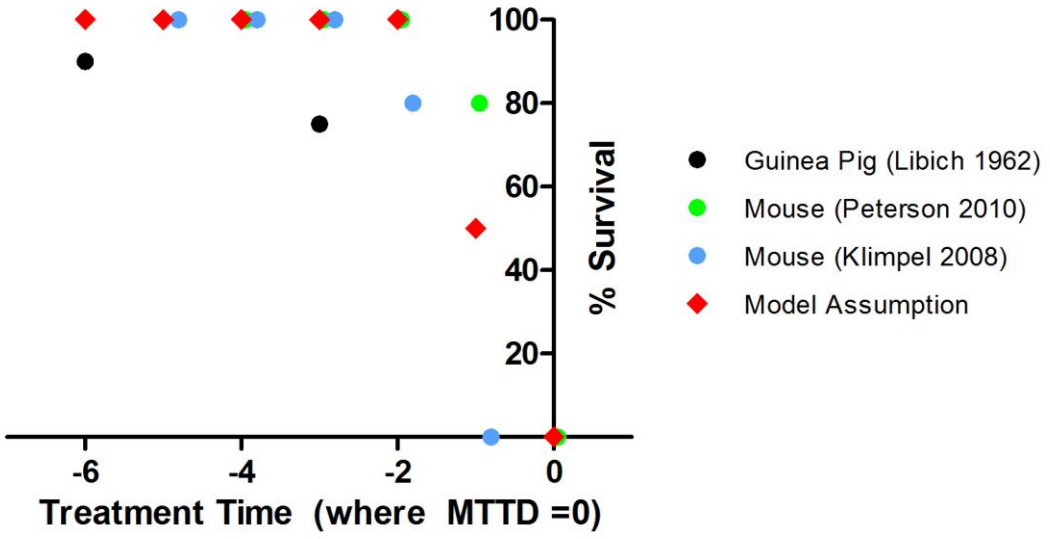

Figure A-3. The survival rate in three animal studies after treatment at various times (relative to the mean time of death of control animals) as compared to the assumption on which we base the parameter in our model.

Human Data

Efficacy of Antibiotics

Although the recommended treatment for tularemia is either streptomycin or gentamicin, other antibiotics or multiple antibiotics were often administered to the human patients described in the clinical cases used for our analysis. In order to determine when the first effective treatment was administered, it was important to understand which antibiotics are effective against *F. tularensis*. Table A-8 shows all of the antibiotics that are relevant to our patient analysis and the efficacy of each antibiotic.

Table A-8. Antibiotic Efficacy against *F. tularensis*

Antibiotic	Efficacy against *F. tularensis*	Source
Atovaquone	No information available on atovaquone alone.	N/A
Aureomycin	*F. tularensis* is sensitive in vivo.	Ransmeier 1949[157]
Azithromycin	*F. tularensis* is sensitive in vivo.	Purcell[158]
Cephalosporin class*	Cephalosporins have resulted in treatment failures.	Cross 1993[159]

[157] Ransmeier JC. "The effect of aureomycin against bacterium tularense." *J Clin Invest.* **28**(5 Pt 1). 1949
[158] Purcell BK USAMRIID Bacterial Therapeutics Center Powerpoint Presentation. (*Official use only*.)
[159] Cross JT and Jacobs RF. "Tularemia: treatment failures with outpatient use of ceftriaxone." *Clin Infect Dis.* **17**(6). 1993.

Table A-8. Antibiotic Efficacy against *F. tularensis*		
Antibiotic	**Efficacy against *F. tularensis***	**Source**
Chloramphenicol	CDC recommended.	CDC,[160] Dennis 2001[161]
Ciprofloxacin	CDC recommended.	CDC, Dennis 2001
Clavulanic acid	*F. tularensis* is resistant to beta-lactams.	Physician's Desk Reference[162]
Clindamycin	*F. tularensis* is resistant in vivo.	Alaska 2003[163]
Doxycycline	CDC recommended.	CDC, Dennis 2001
Erythromycin	*F. tularensis* is sensitive in vitro and in clinical use.	Harrell 1990,[164] Urich 2008[165]
Gentamicin	CDC recommended.	CDC, Dennis 2001
Isoniazid	Drug targets mycobacteria.	Marrakchi 2000[166]
Levofloxacin	*F. tularensis* is sensitive in vivo.	Klimpel 2008[167]
Metronidazole	*F. tularensis* is expected to be resistant because metronidazole is used against anaerobic bacteria.	Rxlist.com[168]
Minocycline	Tetracyclines have moderate to good activity against *F. tularensis*	Giguere 2007[169]
Penicillin class**	*F. tularensis* is resistant to beta-lactams.	Physician's Desk Reference
Streptomycin	CDC recommended.	CDC, Dennis 2001
Sulfadiazine	*F. tularensis* is resistant in vivo.	Vasi'lev 1989[170]
Tetracycline	*F. tularensis* is sensitive in vitro and in clinical use.	Ikaheimo 2000,[171] NYC Health[172]

160 CDC. "Emergency Preparedness & Response: Tularemia, Treatment and PEP." July 1, 2005. http://www.bt.cdc.gov/agent/tularemia/tularemia-biological-weapon-abstract.asp#4. Accessed on April 1, 2011.

161 Dennis DT et al. "Consensus Statement: Tularemia as a Biological Weapon: Medical and Public Health Management." *JAMA.* **285**(21). 2001.CDC. "Emergency Preparedness & Response: Tularemia, Treatment and PEP." July 1, 2005. http://www.bt.cdc.gov/agent/tularemia/tularemia-biological-weapon-abstract.asp#4. Accessed on April 1, 2011.

162 "Summaries of Infectious Diseases: Tularemia." *Red Book, Physicians' Desk Reference.* 113th Edition. Thomson Reuters. 2009.

163 "Tularemia in Alaska" State of Alaska Epidemiology Bulletin 31 1997. Grace C "Tularemia" Bioterrisom e-mail Module #8 June 9, 2003.

164 Harrell, RE & Simmons, HF. "Pleuropulmonary Tularemia: Successful Treatment with Erythromycin." *Southern Medical Journal*. **83**(11). 1990.

165 Urich, SK and Petersen, JM. "In Vitro Susceptibility of Isolates of *Francisella tularensis* Types A and B from North America." *Antimicrob Agents Chemother*. **52**(6). 2008.

166 Marrakchi, H, et al. "InhA, a Target of the Antituberculosis Drug Isoniazid, Is Involved in a Mycobacterial Fatty Acid Elongation System, FAS-II" *Microbiology*. **146**(289). 2000.

167 Klimpel GR et al. "Levofloxacin rescues mice from lethal intra-nasal infections with virulent *Francisella tularensis* and induces immunity and production of protective antibody." *Vaccine*. **26**(52). 2008.

168 "Flagyl (metronidazole)." http://www.rxlist.com/cgi/generic/metronidaz_ids.htm. Accessed on June 2, 2011.

169 Giguere, S. 2007. "Tetracyclines and Gylcylcyclines." Antimicrobial Therapy in Veterinary Medicine. 4th ed: 231-240. Blackwell Publishing, 2007.

170 Vasi'lev NT, et al. "Sensitivity spectrum of Francisella tularensis to antibiotics and synthetic antibacterial drugs." *Antibiot Khimioter.* **34**(9).1989.

171 Ikaheimo, I et al. "In Vitro Antibiotic Susceptibility of *Francisella tularensis* Isolated from Humans and Animals." *Journal of Antimicrobial Chemotherapy*. **46**(2). 2000.

Table A-8. Antibiotic Efficacy against *F. tularensis*		
Antibiotic	**Efficacy against *F. tularensis***	**Source**
Tobramycin	The MIC_{90} of tobramycin was 1.5 mg/L.	Ikaheimo 2000[173]
Trimethoprim-sulfamethoxazole	*F. tularensis* is expected to be resistant because trimethoprim and sulfamethoxazole are resistant.	Maurin 2000
Vancomycin	*F. tularensis* is resistant in vitro.	Vasi'lev 1989

Green: Antibiotics proven effective against *F. tularensis* in vivo.

Orange: Antibiotics with moderate efficacy against *F. tularensis.*

Red: Antibiotics proven ineffective against *F. tularensis*.

Blue: Antibiotics with no available information on efficacy against *F. tularensis.*

**The cephalosporin class includes cefaaclor, cefazolin, cefotaxime, ceftriaxone, cephalexin, cephalothin, and cephapirin.*

***The penicillin class includes amoxicillin, ampicillin, carbenicillin, cloxacillin, cyclacillin, dicloxacillin, methicillin, nafcillin, oxacillin, penicillin, piperacillin and ticarcillin-clavulanic acid.*

Determining Human Clinical Case Biovars

As mentioned in the main text, there are two clinically relevant biovars of *F. tularensis.* Our model assumes exposure to Type A *F. tularensis*, which causes a more severe disease than Type B. Unfortunately, biovar is often not reported in clinical cases of tularemia because *F. tularensis* is extremely difficult to culture from patient samples. Therefore, most cases of tularemia are confirmed by serological studies alone. Because these biovars exhibit some geographical restriction, we instead assumed strain type based on the location of the patient. All cases outside of North America were excluded from our analysis, because Type A *F. tularensis* is found exclusively in North America.[174] For cases in North America, we used a report by Staples et al.[175] to determine what locations in the US were most likely to have cases caused by the Type A biovar. Staples et al. report the number of Type A and Type B clinical cases identified by the CDC between 1964 and 2004 with their location.[176] Cases from states in which every report was from Type A bacteria were included in our analysis, while those states in which any reported cases were Type B were excluded. Data from all deaths were included regardless of location, because Type B is not known to cause death.[177] In addition, cases specifically from Martha's Vineyard in Massachusetts were assumed to be Type A because to date, only Type A specimens have

172 New York City Department of Health and Mental Hygiene. "Medical Treatment and Response to Suspected Tularemia: Information for Health Care Providers During Biologic Emergencies" July 2000. http://www.nyc.gov/html/doh/html/cd/tulmd.shtml#seven. Accessed on April 1, 2011.

173 Ikaheimo I, et al. "In vitro antibiotic susceptibility of Francisella tularensis isolated from humans and animals." Journal of Antimicrobial Chemotherapy.46. 2000.

174 Champion MD et al. "Comparative genomic characterization of *Francisella tularensis* strains belonging to low and high virulence subspecies." *PLoS Pathology*. **5**(5). 2009.

175 Staples JE et al. "Epidemiologic and molecular analysis of human tularemia, United States, 1964-2004. *Emerging Infectious Diseases.* **12**(7). 2006.

176 The Center for Disease Control (CDC) keeps records of the tularemia cases since tularemia is a reportable disease.

177 One report that describes a number of deaths after streptomycin treatment was excluded from our analysis, because the information on the dose and duration was inadequate for our analysis. Giddens W et al. "Tularemia: an analysis of one hundred forty-seven cases." *The Journal of the Louisiana State Medical Society: official organ of the Louisiana State Medical Society.* **109**(3). 1957.

been found at that location.[178] Tables A-9 and A-10 give the relevant details of all of the patients included in our analysis of human clinical cases. These details were used to determine the efficacy of streptomycin and gentamicin, respectively.

[178] Feldman et al. "Tularemia on Martha's Vineyard: seroprevalence and occupational risk." *Emerging Infectious Diseases.* **9**(3). 2003.

Table A-9. Streptomycin Treated Human Clinical and Experimental Cases									
Source	**Patient ID**	**Age**	**Exposure Risk**	**Type and/or Pulmonary Symptoms**	**Antibiotic**	**Antibiotic Dose**	**Treatment Time (days after symptom onset)**	**Treatment Duration (days)**	**Relapse and Fever Notes**
Atwell 1946[179]	1	13	Ticks, rabbits	Pulmonary; cough, rales, pleural effusion, pneumonitis	Sulfadiazine				Thorancentesis performed
					Penicillin	940,000 units total	15	6	
					Streptomycin	5 g/day IM; gradual decrease; total 29.5 g; 1 g IP	19	11	
					Penicillin			14	
	2	17	Ticks, rabbits	Pulmonary; cough, rales	Penicillin	IV and IM; 940,000 units total	3		
					Streptomycin	13 g total IM every 2 hrs	8	8	
Beisel 1967[180]	In this experimental study, human volunteers inhaled aerosolized *F. tularensis* strain SCHU-S4. Of the patients tested, 13 had a "typical" tularemia response (versus mild) and were treated with 1 g of streptomycin every 12 hours for 14 days. Volunteers were treated within 24 hours of presenting with a temperature exceeding 101^{0}F. All volunteers recovered without complications or sequelae.								
Berson 1948[181]	1			Ulceroglandular	Streptomycin		3	5	
	2			Ulceroglandular	Streptomycin		4	7	
	3			Ulceroglandular	Streptomycin		4	6	
	4			Ulceroglandular	Streptomycin		5	8	
	5			Ulceroglandular	Streptomycin		7	8	
	6			Ulceroglandular	Streptomycin		9	8	
	7			Ulceroglandular	Streptomycin		9	6	
	8			Ulceroglandular	Streptomycin		10	11	
	9			Ulceroglandular	Streptomycin		10	7	
	10			Ulceroglandular	Streptomycin		12	8	
	11			Ulceroglandular	Streptomycin		13	5	
	12			Ulceroglandular	Streptomycin		13	4	
	13			Ulceroglandular	Streptomycin		15	8	
	14			Ulceroglandular	Streptomycin		15	12	
	15			Ulceroglandular	Streptomycin		15	6	
	16	21	Trapper	Ulceroglandular	Streptomycin	0.125 g every 3 hrs; 2 g total	16	2	Relapsed with chills, fever, headache 3 days after first therapy ended
					Streptomycin	0.125 g every 3 hrs; 2 g total	21	2	Relapsed 4 days after second therapy ended
					Streptomycin	1.25 g every 24 hrs	27	6	

179 Atwell RJ and Smith DT. "Primary Tularemia Pneumonia Treated with Streptomycin: Report of Two Cases." *Southern Medical Journal*. 39(11). 1946.

180 Beisel WR et al. "Adrenocortical responses during tularemia in human subjects." *Journal of Clinical Endocrinology & Metabolism.* **27**(1). 1967.

181 Berson RC and Harwell AB. "Streptomycin in the treatment of tularemia." *The American Journal of the Medical Sciences*. **215**(3). 1948.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (days after symptom onset)	Treatment Duration (days)	Relapse and Fever Notes
Berson 1948[182]	17			Ulceroglandular	Streptomycin		16	8	
	18			Ulceroglandular	Streptomycin		17	7	
	19	34	Trapper	Ulceroglandular	Streptomycin	0.125 g every 3 hrs	6	1.5	Relapsed with chills, fever, etc 3 days after first therapy ended
					Streptomycin	1.25 g/day	11	6	
	20			Ulceroglandular	Streptomycin		18	8	
	21			Ulceroglandular	Streptomycin		20	6	
	22			Ulceroglandular	Streptomycin		21	8	
	23			Ulceroglandular	Streptomycin		21	8	
	24			Ulceroglandular	Streptomycin		22	5	
	25			Ulceroglandular	Streptomycin		22	10	
	26			Ulceroglandular	Streptomycin		23	9	
	27			Ulceroglandular	Streptomycin		25	7	
	28			Ulceroglandular	Streptomycin		25	17	
	29			Ulceroglandular	Streptomycin		26	9	
	30			Ulceroglandular	Streptomycin		20	6	
	31			Ulceroglandular	Streptomycin		29	7	
	32			Ulceroglandular	Streptomycin		29	6	
	33			Ulceroglandular	Streptomycin		30	6	
	34			Ulceroglandular	Streptomycin		30	8	
	35			Ulceroglandular	Streptomycin		32		
	36	51	Tailor	Ulceroglandular	Streptomycin	0.04 g every 3 hrs	32	6	
	37			Ulceroglandular	Streptomycin		42	8	
	38	44		Ulceroglandular	Streptomycin	1g/day	42	6	Relapsed with lymph nodes tender and swelling 9 days after first therapy ended
					Streptomycin	1g/day	60	7	
	39			Ulceroglandular	Streptomycin		48	8	
	40	25		Ulceroglandular	Streptomycin	1g/day	19	9	Relapsed with enlarged lymph nodes 2 days after therapy finished
					Streptomycin	1g/day	38	9	
	42			Pleuropulmonary	Streptomycin		9	8	
	43			Pleuropulmonary	Streptomycin		11	8	
	44			Pleuropulmonary	Streptomycin		11	5	
	45			Pleuropulmonary	Streptomycin		12	7	
	46			Pleuropulmonary	Streptomycin		14	7	
	47			Pleuropulmonary	Streptomycin		14	9	
	48			Pleuropulmonary	Streptomycin		15	5	
	49			Pleuropulmonary	Streptomycin		17	6	
	50			Pleuropulmonary	Streptomycin		NR	15	

[182] Berson RC and Harwell AB. "Streptomycin in the treatment of tularemia." *The American Journal of the Medical Sciences*. **215**(3). 1948.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (days after symptom onset)	Treatment Duration (days)	Relapse and Fever Notes
Berson 1948	51			Pleuropulmonary	Streptomycin		23	9	
	52			Pleuropulmonary	Streptomycin		24	18	
	53			Pleuropulmonary	Streptomycin		25	7	Antiserum administered prior to streptomycin
	54			Pleuropulmonary	Streptomycin		28	8	
	55			Pleuropulmonary	Streptomycin		34	13	
	56			Pleuropulmonary	Streptomycin		71	7	
Corwin 1952[183]	41		Skinned a rabbit		Penicillin	50,000 units every 3 hrs		8	
					Aureomycin				Administered day 15 in hospital; later discontinued
					Dihydro-streptomycin				Administered day 15 in hospital; treated until recovery
Cross 1993[184]	2	7		Glandular	Ceftriaxone	IM 50 mg/kg		5	Spiking temperature after ceftriaxone
					Streptomycin			≥ 7	
	3	3		Oropharyngeal	Ceftriaxone	IV 75 mg/kg, 1x daily		3	Dysphasia and dehydration after ceftriaxone
					Streptomycin			≥ 7	
	5	8		Pneumonia	Ceftriaxone	75 mg/kg*d		4	Fever and progressive tachypenia after ceftriaxone
					Streptomycin			≥7	
	6	9		Glandular	Ceftriaxone	IM		7	Fever and node suppuration after ceftriaxone
					Streptomycin			≥7	
	8	17		Glandular / pneumonia	Ceftriaxone	IM/IV		8	Fever and positive blood culture 3 days after ceftriaxone
					Streptomycin			≥7	
Draper 1947[185]	1	40	Skinning rabbits barehanded	Pleuropulmonary, typhoidal; pneumonia	Penicillin	200,000 units	5	5	
					Streptomycin	0.5 g IM every 3 hrs	9	11	Thorancentesis day 21

183 Corwin W and Stubbs S. "Further studies on tularemia in the Ozarks: Review of forty-four cases during a three-year period." *JAMA.* **149**(4). 1952.
184 Cross J and Jacobs R. "Tularemia: treatment failures with outpatient use of ceftriaxone." *Clinical Infectious Diseases.* **17**(6). 1993.
185 Draper A. "Streptomycin in tularemic pneumonia; with two case reports." *North Carolina medical journal.* **8**(7). 1947.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (days after symptom onset)	Treatment Duration (days)	Relapse and Fever Notes
Draper 1947	2	10	Played with a wild rabbit	Pleuropulmonary, typhoidal; pneumonia	Streptomycin	3 g every 24 hrs; decrease to 1 Gm/Day; increased to 1.5 Gm/day	6	8	
Evans 1985[186]	Cases in this study were reported as group data. TYPE: 75% (66 people) ulceroglandular, 25% (22 people) typhoidal. SYMPTOMS: 53 with cutaneous ulcers, 76 with enlarged lymph nodes, 21 had pharyngitis (5 typhoidal, 16 ulceroglandular), 37 had abnormal chest radiographs. STREPTOMYCIN: 30 patients were administered streptomycin, 500 mg IM twice daily for 10-14 days. 2 patients had relapse or complication. One died within 6 hours of first streptomycin dose, the other had a mild inflammatory response after treatment. GENTAMICIN: 6 patients were treated with gentamicin, 1-1.5 mg/kg/day. 2 patients experienced relapse or complication. One initial responder relapsed after six days of antibiotics and was subsequently treated with streptomycin and tetracycline. One patient did not respond well to gentamicin treatment and was switched to streptomycin. CHLORAMPHENICOL: 5 patients were administered chloramphenicol at 1-3 g/day. 3 patients relapsed when drug was stopped and were subsequently cured with streptomycin. TETRACYCLINE: 6 patients were administered tetracycline. 3 patients relapsed and were cured with streptomycin alone (2 patients) or streptomycin and tetracycline (1 patient.)								
	1	40	Rabbit	Ulceroglandular	Penicillin				
					Streptomycin	500 mg IM 2x daily			
	2	3	Tick	Ulceroglandular	Cloxacillin				
					Streptomycin	30 mg/kg/day	10	7	
	5	13	Contaminated water	Pharyngeal	Cefaclor				
					Streptomycin				
	6	72	Tick	Typhoidal	Tetracycline			1	
					Penicillin				
					Streptomycin				
Flax 1963[187]		40			Chloramphenicol	3 g daily	4		
					Streptomycin	1 g daily	4		
Ford Jones 1982[188]	3		Muskrat trapping, skinning		Streptomycin	IM 20 mg/kg/d		8	
	4		Muskrat trapping, skinning		Streptomycin	IM 20 mg/kg/d		8	
	5		Muskrat trapping, skinning		Streptomycin	IM 20 mg/kg/d		8	
Foshay 1947[189]	Cases in this study were reported as group data. TYPE: 37 patients total, 10 described as typhoidal SYMPTOMS: 14 had pneumonia. STREPTOMYCIN. All 37 patients were treated with streptomycin IM, IV or SC every 3-4 hours for 2-17 days. Total dose ranged from 0.64 to 29.5 g. One death occurred, described below.								
		55		Pneumonia	Streptomycin	0.15 g every 5 hrs		15 hrs	Admitted day 4 of symptoms; died day 6 of symptoms

186 Evans M et al. "Tularemia: a 30-year experience with 88 cases." *Medicine.* **64**(4). 1985.
187 Flax, L. "TYPHOIDAL TULAREMIA." *Maryland state medical journal.* **12**(601). 1963.
188 Ford-Jones Let al."" Muskrat fever": two outbreaks of tularemia near Montreal." *Canadian Medical Association Journal.* **127**(4). 1982.
189 Foshay, L. "Treatment of tularemia with streptomycin." *The American Journal of Medicine.* **2**(5). 1947.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (days after symptom onset)	Treatment Duration (days)	Relapse and Fever Notes
Gourdeau 1983[190]		66	Cut thumb & rabbit exposure	Ulceroglandular	Ampicillin	Oral	~3.5	5	
					Streptomycin	500 mg IM every 12 hrs		10	
Hanna 1971[191]		33		Oculoglandular	Penicillin	Oral	4	10	
					Chloramphenicol	Eye drops	4	10	
					Tetracycline		14		
					Streptomycin	1 g IM daily	14	10	
Harrell 1985[192]	1	59	Tick		Streptomycin		2		Defervescence within 16 hrs
					Streptomycin				All illness cleared in 1 week
	2	33	Ticks, rattlesnakes		Streptomycin				Asymptomatic 72 hrs after treatment
Hofinger 2009[193]		21	Landscaper, saw dead rabbits	Tularemic meningitis	Amoxicillin	Oral		1	
					Ceftriaxone sodium		8	4	
					Vancomycin hydrochloride		8	4	
					Chloramphenicol sodium succinate	IV 1 g every 12 hrs	12	14	Clinical improvement after 48 hrs of treatment with streptomycin/chloramphenicol
					Streptomycin sulfate	IV 1 g every 12 hrs	12	14	
					Ciprofloxacin hydrochloride	750 mg twice daily	26	14	
Hunt 1947[194]	1	60		Oral; broncho-pneumonia with pleural effusion	Penicillin				
					Streptomycin	0.6 g daily	14	6	Temperature normal after 4 days
	3	22		Oral; lobar pneumonia	Streptomycin	0.5 g daily	16	5	Thoracentesis performed; asymptomatic after 1 day, afebrile in 3 days, pneumonia resolved in 3 weeks
	6	12	Skinning rabbits	Bronchopneumonia	Streptomycin	IM, 0.45 g daily	41	6	Also displayed encephalitis

190 Gourdeau M et al. "Hepatic abscess complicating ulceroglandular tularemia." *Canadian Medical Association Journal.* **129**(12). 1983.
191 Hanna C and Lyford J. "Tularemia infection of the eye." *Annals of ophthalmology.* **3**(12). 1971.
192 Harrell RE. "Tularemia: emergency department presentation of an infrequently recognized disease." *The American Journal of Emergency Medicine.* **3**(5). 1985.
193 Hofinger DM et al. "Tularemic meningitis in the United States." *Archives of neurology.* **66**(4). 2009.
194 Hunt JS. "Pleuropulmonary tularemia: observations on 12 cases treated with streptomycin." *Annals of Internal Medicine.* **26**(2). 1947.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (days after symptom onset)	Treatment Duration (days)	Relapse and Fever Notes
Jacobs 1985[195]	Cases in this study were reported as group data. TYPE: 48% ulceroglandular, 18% glandular, 1% oculoglandular, 16% pneumonic, 2% oropharyngeal, 7% typhoidal, 8% unclassified. LOCATION: Arkansas. STREPTOMYCIN: 23 children, 18 adults. STREPTOMYCIN + TETRACYCLINE: 4 children, 6 adults. GENTAMICIN: 4 adults, all over 65 years of age. TETRACYCLINE: 4 children, 18 adults. CHLORAMPHENICOL: 4 children (3 relapsed), 2 adults. No deaths reported.								
	1	10	Tick	Pleural effusion, pneumonia	Streptomycin	600 mg every 12 hrs	14	7	
	2	13	Tick		Penicillin		5	5	
					Trimethoprim-sulfamethoxazole		10		Short duration
					Streptomycin	2x daily		10	Administered shortly after administration of another antibiotic (TMP/SMX)
	3	3		Lung infiltrate	Cefazolin		6	7	
					Streptomycin		13	7	Relapsed 1 week after therapy with a fluctuant node; node was drained; no further complications or treatment
	4	8		Conjunctivitis, hemorrhage, lymphadenitis	Gentamicin	Topical			
					Cephalexin	Oral			
					Streptomycin			14	
Johnson 1947[196]	1	59	Rabbit bone stuck in thumb		Penicillin	500,000 units IM	4		
					Streptomycin	0.4 g/day; total 7.2 g	9	18	
	2	28	Punctured finger on rabbit bone	Ulceroglandular	Streptomycin	0.8 g/day	~21	4	Not acutely ill upon hospital admission
					Streptomycin	0.4 g/day	25	3	Relapsed 18 days after discharge with fluctuant mass, normal temperature
				Rales present upon relapse	Streptomycin	1.2 g/day	46		
					Streptomycin	Injected into lymph node			Discharged on 20th hospital day; node enlarged and ruptured after discharge

[195] Jacobs RF et al. "Tularemia in adults and children: a changing presentation." *Pediatrics.* **76**(5). 1985.

[196] Johnson J B et al. "Tularemia Treated With Streptomycin." *The American Journal of the Medical Sciences.* **214**(6). 1947.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (days after symptom onset)	Treatment Duration (days)	Relapse and Fever Notes
Johnson 1947	3	48	Handling rabbits	Rales	Penicillin		5	3	Critically ill upon admission
					Streptomycin	100 mg every 3 hrs	8	16	Drug administration suspended for 9 days due to suspicion of streptomycin fever
					Streptomycin	50 mg every 3 hrs IM			
	4	34	Dressing rabbits	Cough, rales	Streptomycin	50 mg every 3 hrs IM	~23	2.5	
					Streptomycin	100 mg every 3 hrs; 11.8 g total	26	~14.75	
					Thiamin chloride	200 mg IM every 3 hrs			
					Penicillin				For intercurrent infection
	5	25	Rabbits		Streptomycin	100 mg every 3 hrs	~63	21	Patient was 3.5 months pregnant; developed symptoms of a "threatening abortion."
					Streptomycin	Injected into node	~70		Administered three times in 7 days
Levy 1950[197]	1	6		Pharyngotonsillar	Streptomycin	250 mg stat; then 125 mg q. 3 hrs	15	6	Afebrile in 24 hrs
	2	4		Ulceroglandular septic	Streptomycin	300 mg stat, then 125 mg q. 3 hrs	8	8	Afebrile in 72 hrs
	3	6	Rabbit and squirrel ingestion	Typhoidal	Penicillin	50,000 units stat; 30,000 units q 3 h			
					Streptomycin	200 mg stat; then 100 mg x 14; 200 mg q 3 hrs	6	7	Afebrile in 48 hrs
	4	5		Paryngotonsillar septic	Streptomycin	400 mg stat; then 200 mg q 3 h	8	9	Afebrile in 48 hrs
	5	3	Tick bite	Pharyngotonsillar	Penicillin				
					Streptomycin	125 mg q 3 hrs	6	10	Afebrile in 12 hrs
	6	10		Ulceroglandular	Streptomycin	125 mg q 3 hrs	14	4	Afebrile in 12 hrs
	7	5		Ulceroglandular septic	Streptomycin	150 mg q 3 hrs	30	7	Afebrile in 12 hrs
	8	4		Pharyngotonsillar septic	Streptomycin	125 mg q 3 h x 16; 200 mg q 3 h x 21	8	9	Afebrile after 24 hrs of larger dose
	9	5		Pharyngotonsillar septic	Streptomycin	125 mg q 3 h x 16; 200 mg q 3 h x 21	8	9	Afebrile after 48 hrs of larger dose
	10	6		Ulceroglandular	Streptomycin	150 mg q 3 hrs	17	5	Afebrile in 48 hrs
	11	8		Ulceroglandular	Streptomycin	125 mg q 3 hrs	10	5	Afebrile in 48 hrs
	12	11		Ulceroglandular	Streptomycin	125 mg q 3 hrs	12	5	Afebrile in 48 hrs

[197] Levy H et al. "Streptomycin Therapy for Childhood Tularemia." *New Orleans Medical and Surgical Journal.* **103**. 1950.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (days after symptom onset)	Treatment Duration (days)	Relapse and Fever Notes
Levy 1950	13	11		Ulceroglandular	Streptomycin	150 mg q 3 hrs	12	10	Afebrile in 72 hrs
	14	5		Glandular	Streptomycin	200 mg q 3 h x 24; 200 mg q 6 h x 16	15	7	Afebrile admission; no node change; questionable relapse
	15	8		Ulceroglandular septic	Streptomycin	150 mg q 3 h x 64	12	8	Presumed relapse
					Streptomycin	125 mg q 6 h x 16	35	4	
	16	4		Ulceroglandular septic	Streptomycin	125 mg q 3 h; 125 mg q 3 h x 32	5	6	Afebrile in 96 hrs
	17	10		Ulceroglandular	Streptomycin	50 mg q 3 h x 64	23	12	Afebrile in 48 hrs
	18	8		Ulceroglandular	Streptomycin	150 mg q 3 h	17	8	Afebrile on admission
	19	12		Glandular	Streptomycin	125 mg q 3 h	14	9	Afebrile in 48 hrs
	20	11		Glandular	Streptomycin	125 mg q 3 h	27	5	Afebrile in 48 hrs
	21	5		Typhoidal	Streptomycin	125 mg q 3 h	6	5	Afebrile in 36 hrs
	22	11		Typhoidal	Streptomycin	125 mg q 3 h	6	5	Afebrile in 24 hrs
	23	11		Glandular	Streptomycin	125 mg q 3 h	16	6	Afebrile on admission
	24	9		Ulceroglandular	Streptomycin	125 mg q 3 h	8	10	Afebrile in 12 hrs
Martone 1979[198]	1	38	Likely aerosol from rabbit		Cephalothin sodium		12	3	
					Tetracycline		15		
					Streptomycin sulfate		17		Afebrile within 1 day
	2	38	Likely aerosol from rabbit		Ampicillin		8	4	
					Doxycycline hyclate		12		
					Streptomycin		19		
	3	35	Likely aerosol from rabbit		Penicillin G procaine				Administered during first week of illness
					Ampicillin				Administered during first week of illness
					Doxycycline		10		Afebrile after 6 days
					Streptomycin		21		
Mason 1980[199]	3	65	Ticks		Penicillin G				
					Ampicillin				
					Ampicillin		7		
					Cephalothin		7		
					Gentamicin	5 mg/kg/day	12	1.5	
					Streptomycin		14		

198 Martone W et al. "Tularemia pneumonia in Washington, DC: a report of three cases with possible common-source exposures." *JAMA.* **242**(21). 1979.

199 Mason W et al. "Treatment of tularemia, including pulmonary tularemia, with gentamicin." *The American review of respiratory disease.* **121**(1). 1980.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (days after symptom onset)	Treatment Duration (days)	Relapse and Fever Notes
McCarthy 1990[200]		13	Lawnmower over rabbit		Amoxicillin	Oral?			
					Clavulanic acid	Oral?			
					Streptomycin	IM	~30		
Magee 1989[201]		16 mo	Bitten by a squirrel		Cephalexin	Oral 77 mg/kg/day divided every 6 hrs	4	6	
					Penicillin G	IV 100,000 units/kg/day divided every 6 hrs			
					Streptomycin sulfate	30 mg/kg/day divided every 12 hrs		3	
					Streptomycin	15 mg/kg/day		3	Two days as outpatient
Miller 1969[202]	Cases in this study were reported as group data. TYPE: 14 ulceroglandular, 14 typhoidal, 1 glandular. EXPOSURE RISK: 18 tick related, 6 animal infection, 5 no vector. SYMPTOMS: All patients had pulmonary involvement. STREPTOMYCIN: 28 patients were treated with streptomycin and recovered completely after a single course. 1 patient was not treated with antibiotics and subsequently died.								
	2	46		Lung infiltrates	Isoniazid				
					Streptomycin				
	3	11	Exposed to sick rabbit		Streptomycin				
	4	63	Ticks	Pleural effusion	Antimicrobials				
					Streptomycin				
	5	34		Bronchopneumonia	Streptomycin				
	6	59		Mediastinal mass, parenchymal involvement	Streptomycin				
Noojin 1947[203]	SM	73	Skinned wild rabbit, scratched wrist	Ulceroglandular/Pulmonary; rales	Penicillin	500,000 units every 3 hrs			>1 week after symptom onset; temperature normal on 3rd hospital day
					Streptomycin	0.5 g IM every 3 hrs		4	>1 week after symptom onset
					Streptomycin	0.3 g IM every 3 hrs		7	
Pekarek 1969[204]	In this experimental study of iron metabolism after tularemia infection, four unvaccinated volunteers served as controls. Two received 2,500 organisms of *F. tularensis* strain SCHU-S4, and two received 25,000organisms. Two (one of each dose) contracted typical disease; two (one of each dose) contracted mild disease. All were given one gram of streptomycin IM twice daily beginning on the day of symptom onset and continuing for seven days. All volunteers recovered quickly and without complication.								

200 McCarthy V and Murphy M. "Lawnmower tularemia." *The Pediatric infectious disease journal*. **9**(4). 1990.
201 Magee J et al. "Tularemia transmitted by a squirrel bite." *Pediatric Infectious Disease Journal.* **8**(2). 1989.
202 Miller R and Bates J. "Pleuropulmonary tularemia. A review of 29 patients." *The American review of respiratory disease*. **99**(1). 1969.
203 Noojin RO and Burleson PW. "Tularemia: Report of An Unusual Case Treated With Streptomycin." *Southern medical journal.* **40**(11). 1947.
204 Pekarek R et al. "The effects of *Francisella tularensis* infection on iron metabolism in man." *The American Journal of the Medical Sciences.* **258**(1). 1969.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (days after symptom onset)	Treatment Duration (days)	Relapse and Fever Notes
Penn 1987[205]	Cases in this study were reported as group data, which was analyzed in two groups. Group A had an acceptable outcome (symptoms resolved in less than one week after treatment) and group B had an unacceptable outcome (prolonged or fatal illness.) GROUP A: 12/12 patients received streptomycin or streptomycin in combination with tetracycline. All survived, and no relapse was mentioned. GROUP B: 5 received streptomycin, none with relapse. 2 received gentamicin, none with relapse. 7 received tetracycline; 2 who received tetracycline for less than one week relapsed. 1 patient received cephalosporin and died 2 days after admission. 1 patient never received appropriate therapy.								
Rosenthal 1951[206]	Cases in this study were reported as group data. TYPE: 44 ulceroglandular, 4 glandular, 3 typhoidal, 1 oculoglandular, 1 combined anginal/typhoidal, 1 not reported. SYMPTOMS: 14 with pneumonia, 4 with pleural effusion. EXPOSURE RISK: 44 with rabbit exposure, 4 with tick exposure, 4 unknown. STREPTOMYCIN: Total of 0.1-64 g, average 14.4 g administered day 1-day 60 of symptoms. Two deaths (which were not included in our analysis as explained previously): one patient died after treatment on 31st day of disease with pulmonic and cerebral complications; one died after receiving therapy on 9th day of disease with diabetes complications. Average morbidity of 3.5 days after streptomycin was initiated, range of 1-9 days. Average hospitalization was 16.4 days, range 3.5-49 days. Therapy injected into nodes proved of no value. One case was never treated.								
Saslaw 1961[207]	In this experimental vaccine study, two unvaccinated human volunteers served as controls. They received 14 and 15 organisms of *F. tularensis* strain SCHU-S4 via inhalation. One gram of streptomycin was administered twice daily, one the day of symptom onset and one the day after symptom onset, and continued for ten days. Both cases recovered completely.								
Shapiro 2008[208]		43	Cleared road debris		Ceftriaxone	IV	7		
					Azithromycin	IV	7		
					Trimethoprim-sulfamethoxazole	IV	7		
					Streptomycin	IV	7	~1	Died ~day 8 of symptoms with cardiac arrest; confirmed Type A
Witherington 1946[209]		32	Killed and skinned rabbits		Penicillin				Administered in the first week of illness
					Sulfadiazine				Administered in the first week of illness
					Streptomycin sulfate	250,000 units; then 100,000 every 4 hrs; total 4,000,000 given	18	~6.25	
Young 1969[210]	Cases in this study were reported as group data. EXPOSURE RISK: Muskrat trapping. SYMPTOMS: 39 patients were symptomatic, 8 patients were asymptomatic but serologically confirmed. 2 had chest pain. STREPTOMYCIN: 2 patients; symptoms abated within 24 hrs. TETRACYCLINE: 18 patients; 4/7 severely ill relapsed or had chronic symptoms after tetracycline. 17 improved after tetracycline. PENICILLIN: 9 patients. UNTREATED: 12 patients. Many patients reported a low-grade fever for several weeks after the end of acute illness.								

Green: Antibiotics proven effective against *F. tularensis* in vivo.
Orange: Antibiotics with moderate efficacy against *F. tularensis.*
Red: Antibiotics proven ineffective against *F. tularensis*.
Blue: Antibiotics with no available information on efficacy against *F. tularensis.*

205 Penn RL and Kinasewitz GT. "Factors associated with a poor outcome in tularemia." *Archives of Internal Medicine.* **147**(2). 1987.
206 Rosenthal J. "Tularemia treated with streptomycin. Analysis of fifty-four cases." *The New Orleans medical and surgical journal.* **103**(11). 1951.
207 Saslaw S et al. "Tularemia vaccine study: II. Respiratory challenge." *Archives of Internal Medicine.* **107**(5). 1961.
208 Shapiro DS and Schwartz DR. "Exposure of Laboratory Workers to *Francisella tularensis* despite a Bioterrorism Procedure." *Journal of Clinical Microbiology.* **40**(6). 2002.
209 Witherington J. "Tularemia treated with streptomycin sulfate." *Memphis medical journal.* **21**(139). 1946.
210 Young LS et al. "Tularemia epidemic: Vermont, 1968." *New England Journal of Medicine.* **280**(23). 1969.

Table A-10. Gentamicin Treated Human Clinical Cases									
Source	**Patient ID**	**Age**	**Exposure Risk**	**Type and/or Pulmonary Symptoms**	**Antibiotic**	**Antibiotic Dose**	**Treatment Time (Days After Symptom Onset)**	**Treatment Duration (Days)**	**Relapse and Fever Notes**
Alford 1972[211]	L.B	76	Unknown	Extensive pulmonary infiltrate	Methicillin		4	1	
					Penicillin		4	1	
					Cephalothin		5	7	
					Gentamicin	60 mg IM every 8 hrs (3 mg/kg/day)	9	12	Fever subsided after 36 hrs treatment, pulmonary infiltrates after 2 weeks gentamicin therapy
Capellan 1993[212]		63	Cat bite	Ulceroglandular; pneumonia symptoms	Penicillin	Oral		3	3 days before hospital admission
					Cloxacillin	Oral		3	3 days before hospital admission
					Penicillin	IV		7	Upon hospital admission
					Cloxacillin	IV		7	Upon hospital admission
					Clindamycin	IV			7 days after hospital admission
					Gentamicin	IV			7 days after hospital admission
CDC 1983[213]	3	50		Primary tularemic pneumonia	Ampicillin		14		
					Gentamicin		16		
Cross 1993[214]	1	2	Tick bites	Glandular / pneumonia	Ceftriaxone	IM, 50 mg/kg, once daily		3	
					Gentamicin	IV, 6.9 mg/kg daily; admin every 8 hrs		7	Fever responded in 24-26 hrs, but relapsed with mandible node 1 week after therapy; node persisted, but no other treatment administered
	7	4		Glandular	Ceftriaxone	IM, 50 mg/kg daily		5	
					Gentamicin			>=7	

211 Alford RJ et al. "Tularemia treated successfully with gentamicin." *The American review of respiratory disease.* **106**(2). 1972.
212 Capellan J and Fong I. "Tularemia from a cat bite: case report and review of feline-associated tularemia." *Clinical Infectious Diseases.* **16**(4). 1993.
213 CDC. "Tularemic Pneumonia – Tennessee." *MMWR Weekly.* **32**(20). 1983.
214 Cross J and Jacobs R. "Tularemia: treatment failures with outpatient use of ceftriaxone." *Clinical Infectious Diseases.* **17**(6). 1993.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (Days After Symptom Onset)	Treatment Duration (Days)	Relapse and Fever Notes
Cross 1995[215]	Cases in this study were reported as group data. TYPE: Primarily ulceroglandular and glandular. EXPOSURE RISK: 22 exposed to ticks or animals, 1 not reported. GENTAMICIN: 23 patients; 87% of which received ineffective antibiotics before gentamicin. Administered on average 12 days after first presenting to a physician. Average 9.5 days duration (range 7-14). Average dose 6 mg/kg/day (range 5.4-7.5) divided every 8 hrs. No relapse occurred.								
Eppes 2003[216]		16	Killed and skinned a wild rabbit	Ulceroglandular	Ticarcillin/ Clavulanic acid		4	1	In hospital
			Cat bite		Dicloxicillin	Oral	5	2	Out of hospital
					Oxacillin	IV	7	3	In hospital
					Gentamicin	IV	7	3	
					Doxycycline	Oral	10		Out of hospital
Evans 1981[217]		22	Cat bite		Gentamicin sulfate				Pregnant, second trimester, no effect on child upon birth, recovered completely
Evans 1985[218]	Cases in this study were reported as group data. TYPE: 75% (66 people) ulceroglandular, 25% (22 people) typhoidal. SYMPTOMS: 53 with cutaneous ulcers, 76 with enlarged lymph nodes, 21 had pharyngitis (5 typhoidal, 16 ulceroglandular), 37 had abnormal chest radiographs. STREPTOMYCIN: 30 patients were administered streptomycin, 500 mg IM twice daily for 10-14 days. 2 patients had relapse or complication. One died within 6 hours of first streptomycin dose; the other had a mild inflammatory response after treatment. GENTAMICIN: 6 patients were treated with gentamicin, 1-1.5 mg/kg/day. 2 patients experienced relapse or complication. One first responder relapsed after six days of antibiotics and was subsequently treated with streptomycin and tetracycline. One did not respond well to gentamicin treatment and was switched to streptomycin. CHLORAMPHENICOL: 5 patients were administered chloramphenicol at 1-3 g/day. 3 patients relapsed when drug was stopped and were subsequently cured with streptomycin. TETRACYCLINE: 6 patients were administered tetracycline. 3 patients relapsed and were cured with streptomycin alone (2 patients) or streptomycin and tetracycline (1 patient.)								
	4	59	Rabbit	Ulceroglandular, eye involvement	Gentamicin	Eye drops	4		
					Gentamicin	3 mg/kg/day	4		
					Cephalothin		4		
Halperin 1985[219]		9.5	Seed in eye. Firecracker spark in eye. Swam in contaminated water. Tick bites. Pet dog.	Oculoglandular	Oxacillin	IV			Upon admission
					Gentamicin	Topical			Upon admission
					Gentamicin	IV		10	Added later
					Chloramphenicol	IV		10	Added later

215 Cross T. "Treatment of tularemia with gentamicin in pediatric patients." *Pediatric Infectious Disease Journal.* **14**(2). 1995.
216 Eppes S. "Tularemia in Delaware: forgotten but not gone." *Delaware medical journal.* **75**(4). 2003.
217 Evans ME et al. "Tularemia and the tomcat." *JAMA.* **246**(12). 1981.
218 Evans M et al. "Tularemia: a 30-year experience with 88 cases." *Medicine.* **64**(4). 1985.
219 Halperin SA et al. "Oculoglandular syndrome caused by Francisella tularensis." *Clinical pediatrics.* **24**(9). 1985.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (Days After Symptom Onset)	Treatment Duration (Days)	Relapse and Fever Notes
Hassoun 2006[220]	1	23	Cat bite	Glandular	Ceftriaxone			2	
					Amoxicillin-clavulanate			14	Relapsed after amoxicillin ceased
					Gentamicin	IV 5 mg/kg/day; adjusted to peak/trough		10	Condition improved significantly in 48 hrs
	2	28	Cat bite	Glandular	Ceftriaxone			1	
					Azithromycin			5	Relapsed after end of azithromycin treatment
					Ceftriaxone			2	
					Amoxicillin-clavulanate			10	Some improvement
					Gentamicin	IV 5 mg/kg/day; adjusted to peak/trough		7	No Relapse
Jackson 1978[221]		59	Cat that brought dead rabbit into the house; subsequently cat died	Chest pain, pneumonia, pleural effusion	Minocycline	Oral; 50 mg every 6 hrs	5	7	
					Cephalothin			1.5	
					Tobramycin			1.5	
					Chloramphenicol				36 hrs later
					Carbenicillin				36 hrs later
					Methicillin		15	1	
					Gentamicin	2 mg/kg every 8 hrs	15	14	
					Methyl-prednisolone	2 g		1	
					Penicillin			7	Returned to work 4 months after symptom onset
					Doxycycline	Oral; 100 mg daily	29	30	No Relapse
Jacobs 1985[222]	Cases in this study were reported as group data. TYPE: 48% ulceoglandular, 18% glandular, 1% oculoglandular, 16% pneumonic, 2% oropharyngeal, 7% typhoidal, 8% unclassified. LOCATION: Arkansas. STREPTOMYCIN: 23 children, 18 adults. STREPTOMYCIN + TETRACYCLINE: 4 children, 6 adults. GENTAMICIN: 4 adults, all over 65 years of age. TETRACYCLINE: 4 children, 18 adults. CHLORAMPHENICOL: 4 children (3 relapsed), 2 adults. No deaths reported.								

220 Hassoun AR et al. "Tularemia and once-daily gentamicin." *Antimicrobial Agents and Chemotherapy*. **50**(2). 2006.

221 Jackson R and Lester J. "Case report. Tularemia presenting as unresponsive pneumonia: diagnosis and therapy with gentamicin." *Journal of the Tennessee Medical Association.* **71**(3). 1978.

222 Jacobs RF et al. "Tularemia in adults and children: a changing presentation." *Pediatrics.* **76**(5). 1985.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (Days After Symptom Onset)	Treatment Duration (Days)	Relapse and Fever Notes
Kaiser 1985[223]	1	58		Ulcer, lymphadenopathy	Penicillin G potassium				Rhabdomyolysis
					Oxacillin sodium				
					Gentamicin sulfate				
Lovell 1986[224]		13 mo.	Cat scratch	Tularemia meningitis	Cyclacillin				
					Ampicillin	IV	41	10	
					Gentamicin	IV	41	10	Relapsed 5 days after therapy was discontinued
					Ampicillin	IV	56	2	
					Chloramphenicol	IV	58	14	
Mason 1980[225]	1	47	No exposure history	Pulmonary; alveolar filling density, pleural effusion	Penicillin	Presumably oral			
					Cephalothin	IV	21	2	
					Gentamicin	5 mg/kg/day	23	10	
	2	77	Ticks	Typhoidal	Penicillin G	IV			
					Gentamicin	3.8 mg/kg/day		10	
	3	65	Ticks	Pulmonary	Penicillin G	Parenteral			
					Ampicillin	Parenteral			
					Ampicillin		7		
					Cephalothin		7		
					Gentamicin	5 mg/kg/day	12	1.5	
					Streptomycin		14		
	4	56	Tick bite	Pulmonary	Ampicillin				
					Gentamicin	3.4 mg/kg/day			Afebrile 24 hrs after treatment
	5	63	Tick bite	Ulceroglandular	Tetracycline	Oral			
					Gentamicin	5 mg/kg/day			
	6	83	Tick bite	Ulceroglandular	Gentamicin	4.7 mg/kg/day		10	
	7	72	Tick bite	Pulmonary	Tetracycline	Presumably oral			
					Gentamicin	5 mg/kg/day			
	8	55	Tick exposure	Pulmonary; with pneumonia	Ampicillin	Oral		6	
					Doxycycline	Oral		6	
					Penicillin G	IV		2	
					Gentamicin	5 mg/kg/day		10	

223 Kaiser AB et al. "Tularemia and rhabdomyolysis." *JAMA.* **253**(2). 1985.
224 Lovell VM et al. "Francisella tularensis meningitis: a rare clinical entity." *The Journal of Infectious Diseases.* **154**(5). 1986.
225 Mason W et al. "Treatment of tularemia, including pulmonary tularemia, with gentamicin." *The American review of respiratory disease.* **121**(1). 1980.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (Days After Symptom Onset)	Treatment Duration (Days)	Relapse and Fever Notes
Mason 1980	9	45	Ate deer; tick exposure	Pulmonary and pericardial; lung infiltrates	Gentamicin	5 mg/kg/day		14	
	10	58	Tick bite	Ulceroglandular	Gentamicin	5 mg/kg/day		8	Afebrile in 42 hrs
Marcus 1990[226]		25		Meningitis; bilateral pulmonary infiltrates	Gentamicin sulfate				
					Tetracycline hydrochloride				
Matyas 2007[227]		33	Landscaper in Martha's Vineyard	Pneumonic	Amoxicillin	Oral	3	1	
					Ceftriaxone	Presumably IV	4	1	
					Atovaquone	Presumably IV	4	1	
					Azithromycin	Presumably IV	4	1	
					Gentamicin	Presumably IV	5	3	
					Doxycycline	Presumably IV	5	2	
					Gentamicin	Daily, outpatient	8	7	
		24	Landscaper in Martha's Vineyard	Pneumonic	Amoxicillin	Presumably oral	1	1	
					Gentamicin	Presumably oral	4	10	
					Doxycycline	Presumably oral	4	10	
		49	Landscaper in Martha's Vineyard	Pneumonic	Amoxicillin	Oral	4		
					Gentamicin	Presumably IV 100 mg every 8 hrs, dose increased day 11 and day 13 to 5.75 mg/kg/day	5	>= 7	
					Doxycycline	Presumably IV	5		
Penn 1987[228]	Cases in this study were reported as group data, which was analyzed in two groups. Group A had an acceptable outcome (symptoms resolved in less than one week after treatment) and group B had an unacceptable outcome (prolonged or fatal illness.) GROUP A: 12/12 patients received streptomycin or streptomycin in combination with tetracycline. All survived, and no relapse was mentioned. GROUP B: 5 received streptomycin, none with relapse. 2 received gentamicin, none with relapse. 7 received tetracycline; 2 who received tetracycline for less than one week relapsed. 1 patient received cephalosporin and died 2 days after admission. 1 patient never received appropriate therapy.								
Provenza 1986[229]	1	57	Unknown	Lung infiltrates	Cephapirin				
					Gentamicin				
	3	51	Tick bites	Lung infiltrates	Ampicillin	At hospital	~7	~14	
					Gentamicin	At hospital		~14	

[226] Marcus DM et al. "Typhoidal tularemia." *Archives of ophthalmology.* **108**(1). 1990.

[227] Matyas BT et al. "Pneumonic Tularemia on Martha's Vineyard: Clinical, Epidemiologic, and Ecological Characteristics." *Annals of the New York Academy of Sciences.* **1105**(1). 2007.

[228] Penn RL and Kinasewitz GT. "Factors associated with a poor outcome in tularemia." *Archives of Internal Medicine.* **147**(2). 1987.

[229] Provenza JS et al. "Isolation of Francisella tularensis from blood." *Journal of Clinical Microbiology.* **24**(3). 1986.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (Days After Symptom Onset)	Treatment Duration (Days)	Relapse and Fever Notes
Risi 1995[230]		44	Insect bite	Ulceroglandular	Amoxicillin/ clavulanate	250 mg 3x daily		10	
					Tetracycline	500 mg 4x daily		10	Admin after amoxicillin was discontinued
					Ceftriaxone	1 g			Admin after tetracycline was discontinued
					Dicloxacillin	500 mg 4x daily			Admin after ceftriaxone was discontinued
					Gentamicin	IV 4 mg/kg/day; 2 doses daily		10	
					Gentamicin	5 mg/kg once daily		14	Relapsed 10 days later with groin pain, fatigue, chills, fluctuant bubo
					Ciprofloxacin	Oral, 750 mg 2x daily		28	Complete recovery after ciprofloxacin
Rodgers 1998[231]	KH	4	Tick bite	Tularemia meningitis	Ceftriaxone	IM, 1 dose	2	1	
					Amoxicillin	Oral	2	1	
					Nafcillin	IV	3	6	
					Cefotaxime	IV	3	6	
					Clindamycin	IV	9	1	
					Gentamicin	IV	9	1	
					Cefotaxime		10	5	
					Vancomycin		10	5	
					Gentamicin	6 mg/kg/day	15	10	
					Doxycycline	4 mg/kg/day; oral	15	21	
Snowden 2010[232]	Cases in this study were reported as group data. TYPE: 17 ulceroglandular (1 with meningitis and pneumonia), 13 glandular. EXPOSURE RISK: 19 with tick bites, 3 with rabbit exposure. GENTAMICIN: 28 patients, for a duration of 6-14 days; 16 completely resolved; 3 had persistence or recurrence of symptoms after 1 week gentamicin and 1 week oral doxycycline. One patient relapsed after 14 days of IV gentamicin treatment (begun 30 days after symptom onset) with persistent lymphadenopathy and required prolonged oral doxycycline treatment. CIPROFLOXACIN: 1 patient was treated with oral ciprofloxacin alone, relapsed, and then was treated with IV gentamicin. DOXYCYCLINE: 1 patient was treated with oral doxycycline, relapsed, and then was treated with IV gentamicin. 4 patients received doxycycline alone with no improvement of symptoms before gentamicin therapy.								

230 Risi GF and Pombo DJ. "Relapse of tularemia after aminoglycoside therapy: case report and discussion of therapeutic options." *Clinical Infectious Diseases.* **20**(1). 1995.

231 Rodgers BL et al. "Tularemic meningitis." *The Pediatric infectious disease journal.* **17**(5). 1998.

232 Snowden J and Stovall S. "Tularemia: Retrospective Review of 10 Years' Experience in Arkansas." *Clinical pediatrics.* **50**(1). 2011.

Source	Patient ID	Age	Exposure Risk	Type and/or Pulmonary Symptoms	Antibiotic	Antibiotic Dose	Treatment Time (Days After Symptom Onset)	Treatment Duration (Days)	Relapse and Fever Notes
Steinmann 1999[233]		82	Tick bite	Oculoglandular	Doxycyline hyclate	2x daily	21	21	
					Gentamicin sulfate	Topical, hourly	21		Patient required cornea and lens implant
Tarpay 1983[234]	1			Pharyngeal	Gentamicin	IV			
	2			Pharyngeal	Gentamicin	IV			

Green: Antibiotics proven effective against *F. tularensis* in vivo.
Orange: Antibiotics with moderate efficacy against *F. tularensis.*
Red: Antibiotics proven ineffective against *F. tularensis*.
Blue: Antibiotics with no available information on efficacy against *F. tularensis.*

233 Steinemann TL et al. "Oculoglandular tularemia." *Archives of ophthalmology.* **117**(1). 1999.
234 Tarpay M. "Tularemic pharyngitis." *Pediatric infectious disease.* **2**(3).1983.

Rate of Relapse

Table A-11 shows the treatment duration and time until relapse of cases extracted from Tables A-9 and A-10 (see above). Patients relapsed in twelve of 432 cases in which the patient was treated with either streptomycin or gentamicin (including 19 experimental and 413 naturally exposed patients), giving a relapse rate of 2.23%. (Four of the twelve relapsed patients were not of military age (18-62 years old), so were not included in the analysis.[235]) Although the majority of the patients who relapsed were treated with antibiotics for fewer than the recommended 10 days, three patients did receive antibiotics for 10 days or more; however, these three patients all had extenuating circumstances. One patient relapsed despite receiving 24 days of IV gentamicin, which might indicate natural resistance of that specific *F. tularensis* strain to gentamicin.[236] The two other patients were treated unusually late in the symptomatic period: one 30 days after symptoms onset, another (a 13-month-old infant) 41 days after symptom onset.[237,238] In addition, it is likely that there is a bias in the clinical literature that favors publishing unusual or severe cases. For these reasons, this value for this parameter is based on the more conservative relapse rate of 2%.

Table A-11. Relapse after Antibiotic Treatment*

Source	Age (Years)	Treatment Duration (Days)	Time Until Relapse (Days)
Berson 1948	34	1.5	3
Berson 1948†	21	2 2	3 4
Berson 1948	44	6	9
Berson 1948	25	9	2
Cross 1993‡	2	7	7
Evans 1985	NR	6	NR
Jacobs 1985‡	3	7	7
Johnson 1947	28	7	18
Levy 1950‡	8	8	NR
Lovell 1986‡	13 mo.	10	5
Risi 1995	44	24	10
Snowden 2010	NR	14	NR
AVERAGE	**21.01**	**7.96**	**6.80**
STANDARD DEVIATION	**16.81**	**5.93**	**4.76**

[235] We define military age as the minimum age for enlistment, 18 years, and the maximum retirement age, 62 based on the following report: "Policy Message 06-06: Change to the Maximum Age Criteria." April 5 2006. http://www.armyreenlistment.com/Messages/Policy/PM_06_06_age.pdf. Accessed on June 2, 2011.

[236] Risi GF and Pombo DJ. "Relapse of tularemia after aminoglycoside therapy: case report and discussion of therapeutic options." *Clinical Infectious Diseases.* **20**(1). 1995.

[237] Snowden J and Stovall S. "Tularemia: Retrospective Review of 10 Years' Experience in Arkansas." *Clinical Pediatrics.* **50**(1). 2011.

[238] Lovell VM et al. "*Francisella tularensis* meningitis: a rare clinical entity." *The Journal of Infectious Diseases.* **154**(5). 1986.

Table A-11. Relapse after Antibiotic Treatment*			
Source	**Age (Years)**	**Treatment Duration (Days)**	**Time Until Relapse (Days)**
NR: not reported. **Relapse data extracted from complete patient information in Tables A-9 and A-10.* *†Patient relapsed twice.* *‡Patients not of military age (18-62 years old).*			

Time to Relapse

The patient data described in Table A-11 above were also used to determine the timing of relapse. We found ten instances of relapse with adequate reports of the time until relapse onset (included in Table A-11). The time to relapse ranged from 2 to 18 days with an average time to relapse of 6.80 days (SD 4.76 days.) These time to relapse data fit a lognormal probability distribution, shown in Figure A-4, which was used in the model to determine the timing of patient relapse.

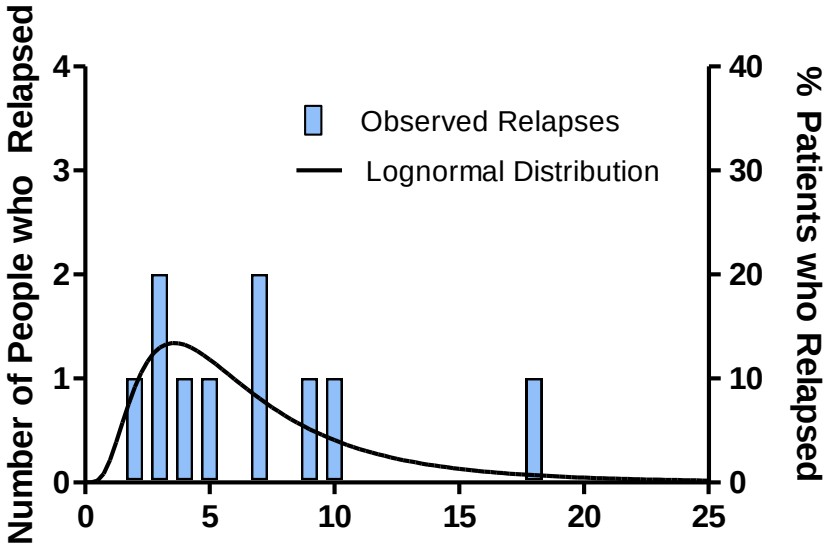

Figure A-4. Number and percent of patients who relapsed after the indicated time. Blue bars indicate the number/percentage of patients (n = 10) for each observed time to relapse.

The length of time between antibiotics being discontinued and relapse is a lognormal distribution shown in the black line in Figure A-4, where σ = 1.71681057 (the mean of the natural logs of the observed values) and μ = 0.665761329 (the standard deviation of the natural logs of the observed values).

Appendix 6. Work Lost

Period of Fever

Individuals that inhale *F. tularensis*, develop tularemia symptoms, and are treated promptly with effective antibiotics typically resolve their fever within a few days of treatment. However, those who do not receive antibiotics in a timely matter (or at all) may take weeks or even months to recover. Table A-12 below summarizes the raw data on the period of time before fever resolves following antibiotic treatment. These human case reports were used to establish the equation describing the duration of fever after treatment with antibiotics.

Table A-12. Patient Data Describing the Period of Time Before Fever Resolves After Treatment With Antibiotics

Day of Symptomatic Period Antibiotics Were Started*	Temperature Before Treatment (^{o}F)	Duration of Fever After Treatment With Antibiotics	Reference
Day 0	104.2	1 day	Feigin and Dangerfield 1967[239]
Day 0	>100	3 days	Sawyer et al. 1966[240]
Day 1	104.6	1 day	Feigin and Dangerfield 1967
Day 1	103.6	1 day	Feigin and Dangerfield 1967
Day 1	102.6	1 day	Feigin and Dangerfield 1967
Day 1	>100	2 days	Sawyer et al. 1966
Day 1	>100	2 days	Sawyer et al. 1966
Day 1	>100	2 days	Sawyer et al. 1966
Day 1	>100	2 days	Sawyer et al. 1966
Day 1	>100	2 days	Sawyer et al. 1966
Day 2	103.2	0 days	Feigin and Dangerfield 1967
Day 2	104.6	1 day	Feigin and Dangerfield 1967
Day 2	103.8	1 day	Feigin and Dangerfield 1967
Day 2	104.2	0 days	Feigin and Dangerfield 1967
Day 2	103.8	1 day	Feigin and Dangerfield 1967
Day 2	105.4	0 days	Feigin and Dangerfield 1967
Day 2	103.8	0 days	Feigin and Dangerfield 1967
Day 2	103.6	0 days	Feigin and Dangerfield 1967

[239] Feign RD and Dangerfield HG. "Whole blood amino acid changes following respiratory-acquired *Pasteurella tularensis* infection in man." *J Infect Dis*. **117**(4). 1967.

[240] Sawyer WD et al. "Antibiotic Prophylaxis and Therapy of Airborne Tularemia." *Bacteriological Reviews*. **30**(3). 1966.

Table A-12. Patient Data Describing the Period of Time Before Fever Resolves After Treatment With Antibiotics			
Day of Symptomatic Period Antibiotics Were Started*	**Temperature Before Treatment (°F)**	**Duration of Fever After Treatment With Antibiotics**	**Reference**
Day 2	102.6	0 days	Feigin and Dangerfield 1967
Day 2	103.6	1 days	Feigin and Dangerfield 1967
Day 3	>100	1 day	Sawyer et al. 1966
Day 4	>100	2 days	Sawyer et al. 1966
Day 5	~102.0	2 days	Parker et al. 1950[241]
Day 7	103.8	10 days	Atwell and Smith 1946[242]
Day 8	104.3	6 days	Berson 1948[243]
Day 10	103.4	2 days	Berson 1948
Day 10	100.5	3 days	Berson 1948
Day 11	103.0	4 days	Berson 1948
Day 13	103.0	3 days	Berson 1948
Day 13	103.0	5 days	Berson 1948
Day 14	103.0	11 days	Berson 1948
Day 18	103.4	2 days	Berson 1948
Day 17	104.5	21 days	Atwell and Smith 1946
Day 22	103.5	7 days	Berson 1948
Day 23	102.6	4 days	Berson 1948
Day 24	102.0	14 days	Berson 1948
Day 27	101.4	1 day	Berson 1948
**Day 0 = day of symptom onset*			

Work Lost in an Individual Who Recovers

Studies on human volunteers infected with *F. tularensis* have been carried out to establish how significantly their work performance is reduced due to tularemia, and to determine when during the disease course an individual is unable to work due to illness.[244,245] Alluisi et al describe work

[241] Parker RT et al. "Use of chloramphenicol (chloromycetin) in experimental and human tularemia." *JAMA.* **143**(1). 1950.
[242] Atwell RJ and Smith DT. "Primary Tularemia Pneumonia Treated with Streptomycin." *Southern Medical Journal.* **30**(11). 1946.
[243] Berson RC. "Streptomycin in the Treatment of Tularemia." *The American Journal of the Medical Sciences*. **215**(3). 1948.
[244] Anno et al. Consequence Analytic Tools for NBC Operations, Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever. Defense Special Weapons Agency. 1998.
[245] Alluisi, Thurmond and Coates. *Behavioral Effects of Infectious Diseases: Respiratory Pasteurella Tularensis, Perceptual and Motor Skills*, Vol. 32. 1971.

performance as the intellectual and physical ability to perform tasks, and Anno et al describe "performance decrement" that results from illness.

Anno et al performed three different tests of performance decrement, which include physical strength (testing the maximum force exerted in a single squeeze of the hand), sensory and cognitive ability (using the Multiple Task Performance Battery which is a synthetic work scenario, like that described by Alluisi et al), and physical endurance (tested by measuring the time period to exhaustion that maximum force could be applied to a hand grip). Results indicated that physical endurance was the ability most affected by illness, and therefore we base our measure of ability to work on physical endurance. Physical endurance decreased ~8.5% per degree of fever.[246] Given that it has been suggested that 60% effectiveness is the lowest level of performance acceptable for a warfighter,[247] a fever between 103°F and 103.5°F would physically incapacitate a warfighter beyond an acceptable level ($100\% - (8.5\% \times (103.4^0F - 98.6^oF)) = 59.2\%$.), however any level of fever may make it difficult for a warfighter to perform his or her duties. Curling et al indicate that high fever occurs during Stage 1 of the symptomatic period and continues through Stage 2.[248] Case studies indicate that fevers associated with tularemia typically exceed 103°F (see Table A-13).[249] Thus, our model assumes individuals are unable to work through both Stage 1 and Stage 2 of the symptomatic period.[250]

In addition to the inability to work during the febrile period, case studies indicate that individuals recover in a period of time equal to approximately 117% of the period of fever. The data supporting this assumption is detailed in Table A-13 (note that work lost is equal to the period of fever plus the recovery period).

Table A-13. Work Lost as a Function of Febrile Period

Period of Fever	Total Period of Time Individuals Unable to Work	Work Lost as A Function of Febrile Period	Reference
11 days	28 days	250%	Berson 1948[251]
14 days	31 days	220%	Rosenthal 1951[252]
23 days	40 days	174%	Berson 1948
29 days	55 days	190%	Berson 1948
29 days	56 days	193%	Foshay 1947[253]
30 days	57 days	190%	Foshay 1947

246 Anno et al. Consequence Analytic Tools for NBC Operations, Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever. Defense Special Weapons Agency. 1998

247 Human Performance Resource Center (HPRC). "How much sleep does a Warfighter need?" http://humanperformanceresourcecenter.org/mind-tactics/hprc-articles/how-much-sleep-does-a-warfighter-need. Accessed on Sept 26, 2011. HPRC is a Department of Defense initiative under the Force Health Protection and Readiness Program.

248 Curling, C et al. "Parameters for Estimation of Casualties from Exposure to Selected Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia. Volume I: DRAFT 02/07/2011. Tularemia Extract." Institute for Defense Analysis (IDA) Document D-4132, November 2010.

249 Table 3-1 from: Anno et al. Consequence Analytic Tools for NBC Operations, Volume 1: Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever. Defense Special Weapons Agency. 1998.

250 Curling, C et al. "Parameters for Estimation of Casualties from Exposure to Selected Biological Agents: Brucellosis, Glanders, Q Fever, SEB and Tularemia. Volume I: DRAFT 02/07/2011. Tularemia Extract." Institute for Defense Analysis (IDA) Document D-4132, November 2010.

251 Berson RC. "Streptomycin in the Treatment of Tularemia." *The American Journal of the Medical Sciences*. **215**(3). 1948.

252 Rosenthal. "Tularemia Treatment with Streptomycin." *New Orleans Med Surg J*. **103**(11). 1951.

253 Foshay L. "Treatment of Tularemia with Streptomycin." *The American Journal of Medicine*. **2**(5). 1947.

Table A-13. Work Lost as a Function of Febrile Period			
Period of Fever	**Total Period of Time Individuals Unable to Work**	**Work Lost as A Function of Febrile Period**	**Reference**
31 days	94 days	303%	Foshay 1947
		Mean 217% SD (45%)	